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Comparative study on effect of different techniques used in the development of chlorthalidone fast dissolving tablets

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ABSTRACT

Attempts were made to prepare fast dissolving tablets of Chlorthalidone by using superdisintegrant, co-grinding with carriers (i.e. Mannitol, PVP), and solid dispersions with the same and by sublimation method. Formulations were evaluated for precompressional parameters such as angle of repose, % compressibility and Hausner's ratio. Tablets were subjected to postcompressional analysis for the parameters such as hardness, friability, in vitro disintegration time, wetting time and dissolution test. Drug compatibility with excipients was checked by FTIR and DSC studies. Stability studies were carried out as per ICH guidelines for three months. The results revealed that tablets prepared by the sublimation method using 40% camphor (F12) significantly enhanced the dissolution rate of drug. Tablets prepared by co-grinding with PVP without Crosspovidone gave inferior dissolution rates. Tablets containing solid dispersions with crospovidone yielded good results in terms of dissolution rate. Mannitol can successfully be used as carrier for both methods. Stability studies revealed that upon storage, disintegration time of tablets prepared with Mannitol increased significantly ($p<0.05$) and that those of prepared with PVP decreased significantly ($p<0.05$).

Key words: Fast dissolving tablet, Chlorthalidone, Crospovidone, solid dispersion, co-grinding, Sublimation.

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INTRODUCTION

Chlorthalidone is a phthalamide derivative of benzene sulphonamide and is designated as 2-chloro-5-(1-hydroxy-3 –oxo-1-isoindolinyl) benzene sulphanilamide. It is white to yellowish crystalline powder. It is practically insoluble in water, slightly soluble in alcohol [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].

The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion) [3]. The dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution.

Now a day fast dissolving tablets are gaining more importance in the market. Currently these tablets are available in the market for treating many disease conditions. More is concerned on hypertension, migraine, dysphasia, nausea and vomiting, Parkinson's disease, schizophrenia, pediatric emergency [4-10]. These conditions are those which require the drug to be formulated as fast dissolving tablets. Some patient prefers fast dissolving tablets to conventional tablets best of ease of administration, swallowing, pleasant taste and the availability in several flavors [11].

The peadiatric and geriatrics patients are of particular concern. To overcome this, dispersible tablets [12] and fast-disintegrating tablets [13] have been developed. Most commonly used methods to prepare these tablets are; freeze-drying/Lyophilization [14] tablet molding [15] and direct-compression methods [16]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in oral cavity [14,17]. The main disadvantages of tablets produced are, in addition to the cost intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug [12]. Moulded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern [18]. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets [19]. Therefore, direct-compression appears to be a better option for manufacturing of tablets. The objective of the present work to develop chlorthalidone fast dissolving tablets prepared by using different techniques. Fast dissolving tablets can be prepared by many methods. In the present work tablets are prepared by direct compression method involving incorporation of co-ground mixtures, solid dispersions (SD) and by sublimation methods. Crospovidone (CP) was used as superdisintegrant. Effect of various concentrations on disintegration time, wetting time, and dissolution was studied. Effect of method of preparation (i.e. co-grinding, solid dispersion and sublimation) on dissolution rate, disintegration time and wetting time was studied. Different formulations were prepared by different techniques compositions of which are given in [Table 1 and 2].

MATERIAL AND METHODS

Chlorthalidone was procured as a gift sample from IPCA Laboratories, Mumbai. Crospovidone was obtained as a gift sample from Maruthi chemicals Ahmedabad. Microcrystalline cellulose, PVP, mannitol, PEG, camphor, magnesium stearate and talc were purchased from S.D. Fine Chemicals. Mumbai. All other materials used were of pharmaceutical grade.

Preparation of tablets containing co-ground mixtures

The drug and hydrophilic carriers (i.e. Mannitol, PVP in ratio of 1:1, 1:2, 1:4 and 2:1) were co-ground with help of mortar and pestle for a fixed time of 15 minutes. Then superdisintegrant and directly compressible diluents were added and the mixture was mixed together (in a plastic container). Magnesium stearate and talc were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend.

Preparation of tablets by sublimation technique

The tablets containing 25 mg of chlorthalidone were prepared by sublimation method and formulae used are shown in Table 2. The drug, directly compressible diluents, super disintegrants and camphor were properly mixed together (in a plastic container). Aerosil, magnesium stearate and talc were passed through mesh no. 60, mixed and blended with initial mixture in a plastic container. The tablets were prepared by direct compression method by manual feeding using 7 mm bi concave punches on a 'Rimek mini press 1' a 10 station rotary compression machine.

After compression the tablets were heated by vacuum drying technique at 50^{o} C until a constant weight was obtained to ensure the complete removal of sublimable component. The sublimable component was removed to make the tablet porous.

Preparation of tablets containing solid dispersions of chlorthalidone

Solid dispersions of chlorthalidone were prepared by solvent evaporation method. Drug was weighed and taken in a china dish, dissolved in methanol and then the carrier was added (i.e. PVP, Mannitol, in ratios of 1:1, 1:2, 1:4 and 2:1, respectively). The solvent was evaporated at room temperature and then dried in hot air oven at 50ºC for four hours. The resultant mass was passed through sieve no. 60 and stored in the desiccator.

The solid dispersions equivalent to 25 mg of drug were taken. Then mixed with directly compressible diluent and superdisintegrants in a plastic container. Magnesium stearate and talc were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend.

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 [20] study tablet was put into 100 ml distilled water at 37 ± 2°C. Time required for complete dispersion of a tablet was measured with the help of digital tablet disintegration test apparatus and in wetting time [21] 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 [22,23] 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^{o}C. 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^{o}C/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°C/ 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 P1 and M1 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 solid dispersions 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°C/min from 50-300°C.

RESULTS AND DISCUSSION

Table 2 shows the pre-compressional parameters of powder blend. In case of solid dispersions Angle of repose ranged from 26.2 to 32.8 in PVP and decreased from 29.1 to 26.9 in Mannitol formulations respective In case of co-grounding angle of repose has no change by using hydrophilic carrier PVP but gradual increase has been noticed by using mannitol as a hydrophilic carrier.

% Compressibility ranged from 13.26 –26.16 in all formulations and in the preparation of solid dispersions of the ratio 1:4 (P3) there is decrease in the flow property as there is change the method of preparation to co-grinding method and to sublimation method. However most of the formulations show good and fair flow properties. Hausner's ratio ranges from 1.15 to 1.35 in all formulations. Most of the formulations show good and fair flow properties.

The data obtained from post-compression parameters such as hardness, friability, thickness, drug content, wetting time, and *in vitro* disintegration.

In all the formulations, hardness test indicated good mechanical strength, tablet prepared with PVP as carrier hardness of the tablet increases as there is increase in the concentration of carrier this may be due to increase in contact area among powder particles [24]. Among all the formulations hardness of the tablet prepared with PVP as a carrier was highest as there is increase in the carrier ratio. The friability is less than 1%, indicated that tablets had a good mechanical resistance. Thickness of the tablets range from 3.28 to 3.95 mm. Tablets prepared with mannitol showed highest thickness because of their least density. The results are shown in [Table 3].

Results of wetting time studies and drug content studies were shown in Table 3. Wetting time of formulations P5, P6, P7 and P8 were significantly higher ($p<0.05$) than other formulations. Wetting time of F11 and F12 decreased ($p<0.05$) as compared to P3 and M3 respectively because of high porosity of tablets [25]18. Drug content of tablets ranged between 96.62 to 104.6%. Table 3 shows the disintegration time of the formulations. By the addition of the superdisintegrant the disintegration time decreased significantly ($p<0.05$). In sublimation method of preparation of tablets the disintegration time decreased regardless of the diluents used. It is because tablets prepared by sublimation method rapidly exhibits high pores and disintegrates rapidly. Tablets prepared with 4% superdisintegrant and 40% camphor showed least disintegration time as compared to all other formulations this is because of their porous structure responsible for faster uptake hence it facilitates wicking action of crospovidone in bringing about faster disintegration [25].

The dissolution of chlorthalidone from tablets is shown in Figures 1 to 7. Table 4 shows the $t_{50\%}$ and $t_{90\%}$ values of release profiles of tablets. The dissolution of the drug from the tablets prepared by Camphor

sublimation method was quicker than those prepared by solid dispersions methods using PVP and Mannitol as carriers. This may be due to their porous structure which is responsible for faster disintegration [25]. Crosspovidone containing tablets rapidly exhibits high capillary activity and pronounced hydration with a little tendency to gel formation [26] and disintegrate the tablets rapidly.

The dissolution rate of tablets prepared with co-grinding using hydrophilic carrier Mannitol in the ratio 1:1, 1:2, and 1:4, was enhanced (F5, F6 and F7) as compared to hydrophilic carrier with PVP in the ratio 1:1, 1:2, and 1:4 (F1, F2 and F3) this may be due to increased hardness of tablet with increase in concentration of PVP and due to late disintegration of tablets when used as a carrier. Finally $t_{50\%}$ and $t_{90\%}$ values of F4 showed significant improvement than F1 this may be due to reduction of drug particle size and hence enhanced effective surface area under milling conditions and enhanced wettability in the presence of a carrier [27]. Formulation of the ratio 1:4 (F3) using hydrophilic carrier PVP gave inferior dissolution rates because of increase in hardness of the tablets and late disintegration times.

The dissolution rates of tablets prepared with solid dispersions of chlorthalidone in the ratio 1:1, 1:2, and 1:4 (P1, P2, P3) with PVP, in the same ratio (M1, M2, M3) with mannitol increased significantly ($p<0.05$) than P5, P6, P7 with PVP and M5, M6, M7 with mannitol respectively, this may be due to the use of crospovidone because of their easy and rapid dispersibility in the aqueous dissolution fluids [28]. In addition to micronization conversion of drug to an amorphous form during the preparation might have also contributed to increase in the dissolution rates observed with the solid dispersions [29].

Figures 1, 2 shows the dissolution profiles of tablets prepared from solid dispersions of chlorthalidone using Crosspovidone as superdisintegrant. The $t_{50\%}$ and $t_{90\%}$ values indicate that the dissolution rates of solid dispersions (P1, P2, P3) increased significantly ($P<0.05$) and dissolution rate is also improved as the amount of the carrier increased.

The pure drug sample Chlorthalidone shown characteristic absorption bands in the following IR region. IR (KBR) cm^{-1}. The broad peak between 3280 to 3400 (OH-hydrogen bonded, NH2 and ring –NH), the peak around 3060 may be due to aromatic C-H stretching. The sharp peak at 1680 -C=0 of the ring 1620, 1560, 1480 C=C ring stretching peak at 730 substituted benzene. The IR spectrum of the formulation P1(1:1) has shown a very broad in the wider range 2880-3400cm^{-1} as this broad band contains several other peaks which corresponds to OH of the drug and PVP hydrogen bonded, -NH & $-NH_2$ of the drug and –CH stretching of $–CH_2$ groups of PVP.

PVP solid dispersions (P1)

The characteristic absorption band at 1680 correspond to the ring –C=O group, though this is a prominent peak instead of sharp it appeared as broad may be due to the reason that the ring –C=O of the drug and PVP appear in the same range. This data clearly indicate that there is no major shift in the positioning of the characteristic absorption bands of the formulation from the pure drug and PVP we can concluded that there is no absolutely interaction of the drug and with the PVP and both components are retained their identity in the formulation.

Mannitol solid dispersions

The formulation M1 (1:1) shows the characteristic absorption bands in the following IR region. The broad peak in the range 3280-3400 shows the presence of –OH hydrogen bonded of both drug and Mannitol. -NH2 and NH of drug 2960. The peak at 3160 is an aromatic –CH stretching of the drug however peaks at 2880, 2960 –CH stretching of Mannitol. The sharp peak at 1680 may be ring C=O of the drug molecule.

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 the Mannitol used for the formulation.

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^{o}C. The melting point of the compound from its thermogram is in agreement with the theoretical melting point of the drug. The sharp melting point justifies the purity of the compound.

The formulation of this drug with the polymer PVP is the solid dispersion P3 (1:4). The DSC thermogram of the solid dispersion obtained from its thermal analysis reveals that there is no marked change in the melting point of the pure drug in its solid dispersion form. The melting point is in the range of 222^{o}C which is in the permissible range. The thermal study of the thermograms reveals that the sharpness of the thermogram of the pure drug is reduced and appeared as a broad peak showing the melting point of the solid dispersion almost near to the melting point of the pure drug. As the peak height is reduced and has become more broad in nature indicates that there is a change in the physical state of the pure drug from its crystalline nature to amorphous, so the change from crystalline to amorphous nature is a characteristic property of the drug showing increase in the solubility of the drug. So therefore we can conclude that the solubility of the drug in the dosage form is much higher than the pure drug.

Further as there is no change in the melting point of the drug in its pure form and in its dosage form clearly reveals that there is no interaction of the drug with the polymer .the same was observed with the dosage form of the drug M3 (1:4).

Table 5 shows the parameters of tablets after stability studies. The increase in the disintegration time was observed in case of tablets prepared with Mannitol. This may be due to increase in the hardness of the tablets during storage as reported by Nuguru et al 27-29]. Decrease in the disintegration time was observed in tablets prepared with PVP. This may be due to high hygroscopic nature of the PVP which may be responsible for softening of tablets. No significant changes in the thickness were observed in tablets prepared with Mannitol, PVP, and drug content of all formulations was within the acceptable limits.

CONCLUSION

From this study, it can be concluded that dissolution rate of Chlorthalidone tablets could be enhanced by using superdisintegrant, sublimation, co-grinding it with hydrophilic carriers like PVP and Mannitol or by solid dispersion technique with the same. Tablets with solid dispersion of different ratios with the same carriers without superdisintegrants (P5, P6 and P7) gave inferior dissolution rates than solid dispersion of different ratios with superdisintegrants (P1, P2 and P3).

Finally it can be concluded that the superdisintegrant had played an important role to decrease disintegration time and to enhance the dissolution rate in solid dispersion and co-grinding techniques. Among all the methods the sublimation method was the best technique, hence could be used to prepare the Fast Dissolving Tablets.

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Table 1: Formulae used in the preparation of tablets containing solid dispersion with superdisintegrant

Formulation code	Amount of SD equivalent to 25 mg of drug (with PVP and CP)	Amount of SD equivalent to 25 mg of drug (with Mannitol and CP)	Amount of SD equivalent to 25 mg of drug (with PVP and without CP)	Amount of SD equivalent to 25 mg of drug (with Mannitol and without CP)	MCC
P1	56.42	--	---	--	87.58
P2	79.26	--	--	--	64.74
P3	116.0	--	--	--	28.00
P4	36.26	--	--	--	107.74
M1	--	37.8	--	--	106.20
M2	--	40.3	--	--	103.70
M3	--	51.81	--	--	92.14
M4	--	26.92	--	--	117.00
P5	--	--	55.48	--	88.52
P6	--	--	77.5	--	66.50
P7	--	--	114.0	--	30.00
P8	--	--	35.25	--	111.45
M5	--	--	--	36.7	107.3
M6	--	--	--	42.4	101.6
M7	--	--	--	52.75	91.25
M8	--	--	--	25.85	118.15

** All the formulations contain 3 mg of crosspovidone and 1.5 mg of magnesium stearate, and talc.

Table 2: Formulae used in the preparation of tablets containing co-ground method and camphor by sublimation technique

Formulation code	Chlorthalidone	PVP co-ground	Mannitol co-ground	Spray dried lactose	Directly compressible M.C.C.	Camphor	Aerosil	MCC
F1	25	025.00	--	--	--	--	--	94.00
F2	25	050.00	--	--	--	--	--	69.00
F3	25	100.00	--	--	--	--	--	19.00
F4	25	012.50	--	--	--	--	--	106.50
F5	25	--	025.00	--	--	--	--	94.00
F6	25	--	050.00	--	--	--	--	69.00
F7	25	--	100.00	--	--	--	--	19.00
F8	25	--	012.50	--	--	--	--	106.50
F9	25	--	--	74.00	30.00	7.5	1.5	--
F10	25	--	--	66.50	30.00	15	1.5	--
F11	25	--	--	51.50	30.00	30	1.5	--
F12	25	--	--	21.50	30.00	60	1.5	--

** The formulations F1 to F8 contain 3 mg of crosspovidone and 1.5 mg of magnesium stearate, and talc.
*** The formulations F9 to F12 contain 6 mg of crosspovidone and 3 mg of magnesium stearate, and talc.

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Table 2: Precompressional parameters

Formulation	Angle of Repose (θ) (±SD), n=3	Compressibility (%) (±SD), n=3	Hausner's Ratio (±SD), n=3
P1	26.0 ± 0.61	21.82 ± 0.50	1.27 ± 0.005
P2	27.5 ± 0.47	24.27 ± 0.62	1.32 ± 0.01
P3	31.0 ± 0.23	22.60 ± 1.96	1.28 ± 0.02
P4	32.8 ± 0.17	25.70 ± 1.03	1.33 ± 0.02
E1	29.1 ± 0.11	24.26 ± 0.63	1.32 ± 0.01
E2	24.9 ± 0.46	26.16 ± 1.16	1.35 ± 0.01
E3	27.4 ± 0.05	20.28 ± 0.69	1.26 ± 0.01
E4	26.9 ± 0.80	26.00 ± 0.52	1.35 ± 0.005
P5	27.5 ± 0.45	24.27 ± 0.62	1.32 ± 0.01
P6	26.2 ± 0.61	21.84 ± 0.48	1.27 ± 0.005
P7	24.9 ± 0.46	26.16 ± 1.16	1.35 ± 0.01
P8	24.5 ± 0.24	13.26 ± 0.40	1.16 ± 0.01
E5	25.8 ± 0.28	23.46 ± 0.92	1.26 ± 0.01
E6	25.6 ± 0.28	24.18 ± 0.19	1.31 ± 0.005
E7	27.1 ± 0.57	20.08 ± 1.38	1.3 ±0 .01
E8	24.5 ± 0.24	13.26 ± 0.40	1.33 ± 0.00
F1	25.0 ± 0.05	25.00 ± 0.00	1.3 ± 0.01
F2	27.1 ± 0.57	20.08 ± 1. 38	1.3 ± 0.01
F3	25.8 ± 0.28	23.46 ± 0.92	1.26 ± 0.01
F4	27.2 ± 0.51	21.00 ± 1.03	1.26 ± 0.01
F5	24.5 ± 0.24	13.26 ± 0.40	1.15 ± 0.005
F6	25.7 ± 0.14	14.00 ± 0.86	1.16 ± 0.01
F7	27.5 ± 0.08	25.13 ± 1.27	1.32 ± 0.03
F8	28.1 ± 0.71	13.76 ± 1.07	1.15 ± 0.02
F9	22.1 ± 0.11	23.67 ± 0.40	1.31 ± 0.00
F10	25.6 ± 0.28	24.18 ± 0.19	1.31 ± 0.005
F11	26.6 ± 0.51	24.50 ± 0.17	1.32 ± 0.03
F12	27.4 ± 0.05	26.06 ± 0.57	1.35 ± 0.005

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

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Table 3:- Post-compressional parameters of tablets

Formulation	Hardness Test (kg/cm) ± SD, n=6	Friability (%) ± SD, n=6	Thickness (mm) ± SD, n=6	Disintegration Time (sec) ± SD, n=6	Wetting Time (sec) ± SD, n=6
P1	3.25 ± 0.25	0.33 ± 0.00	3.75 ± 0.15	18.70 ± 0.30	14.60 ± 0.57
P2	3.42 ± 0.38	0.49 ± 0.03	3.88 ± 0.18	15.72 ± 1.15	14.92 ± 1.58
P3	4.50 ± 0.25	0.44 ± 0.10	3.28 ± 0.15	13.33 ± 1.52	9.54 ± 1.65
P4	3.42 ± 0.38	0.41 ± 0.04	3.68 ± 0.18	28.00 ± 1.28	18.33 ± 0.57
E1	4.25 ± 0.25	0.26 ± 0.06	3.82 ± 0.17	23.25 ± 1.65	19.33 ± 0.57
E2	3.25 ± 0.25	0.37 ± 0.07	3.75 ± 0.15	21.24 ± 1.36	13.66 ± 0.57
E3	3.42 ± 0.14	0.51 ± 0.07	3.68 ± 0.15	18.30 ± 0.57	9.33 ± 0.57
E4	4.25 ± 0.25	0.63 ± 0.04	3.95 ± 0.13	26.42 ± 1.85	20.33 ± 0.57
P5	3.42 ± 0.14	0.33 ± 0.00	3.68 ± 0.16	242.00 ± 2.01	229.6 ± 0.57
P6	4.25 ± 0.25	0.54 ± 0.03	3.82 ± 0.16	602.33 ± 1.08	509.66 ± 0.57
P7	5.08 ± 0.14	0.22 ± 0.03	3.84 ± 0.17	903.25 ± 1.57	896.55 ± 0.57
P8	4.42 ± 0.14	0.52 ± 0.06	3.93 ± 0.12	420.33 ± 1.52	410.24 ± 1.25
E5	4.42 ± 0.14	0.44 ± 0.04	3.93 ± 0.16	43.24 ± 1.54	36.66 ± 0.57
E6	4.25 ± 0.25	0.35 ± 0.03	3.70 ± 0.12	37.04 ± 1.87	29.33 ± 0.57
E7	4.42 ± 0.14	0.39 ± 0.17	3.75 ± 0.14	31.66 ± 1.52	20.66 ± 0.57
E8	4.50 ± 0.25	0.61 ± 0.03	3.28 ± 0.15	55.33 ± 0.57	47.33 ± 0.57
F1	3.42 ± 0.14	0.52 ± 0.00	3.52 ± 0.13	23.87 ± 1.45	15.66 ± 0.57
F2	4.25 ± 0.25	0.59 ± 0.005	3.95 ± 0.16	181.29 ± 1.54	173.31 ± 1.00
F3	4.50 ± 0.25	0.52 ± 0.005	3.28 ± 0.16	361.22 ± 1.36	343.32 ± 1.00
F4	3.33 ± 0.38	0.59 ± 0.005	3.53 ± 0.16	28.33 ± 0.57	18.66 ± 0.57
F5	3.42 ± 0.38	0.33 ± 0.005	3.52 ± 0.12	25.00 ± 1.00	18.66 ± 0.57
F6	3.25 ± 0.25	0.22 ± 0.034	3.75 ± 0.15	20.87 ± 1.24	13.66 ± 0.57
F7	3.08 ± 0.14	0.53 ± 0.01	3.68 ± 0.17	18.33 ± 0.57	10.33 ± 0.57
F8	3.33 ± 0.14	0.41 ± 0.03	3.53 ± 0.12	27.56 ± 1.87	21.66 ± 0.57
F9	4.13 ± 0.12	0.42 ± 0.04	3.75 ± 0.19	27.68 ± 1.98	19.33 ± 0.57
F10	4.23 ± 0.25	0.2 ± 0.00	3.84 ± 0.15	15.33 ± 0.57	10.66 ± 0.57
F11	4.03 ± 0.26	0.22 ± 0.03	3.80 ± 0.16	11.57 ± 1.35	6.33 ± 0.57
F12	4.02 ± 0.02	0.33 ± 0.00	3.74 ± 0.13	6.00 ± 1.45	2.66 ± 0.57

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

Table 4: dissolution parameters ($t_{50\%}$ and $t_{90\%}$) and drug content of tablets.

Formulation	$t_{50\%}$ (min) ± SD, n=6	$t_{90\%}$ (min) ± SD, n=6	Drug content (%) ± SD, n=6
P1	7.58 ± 2.4	11.16 ± 1.9	103.32 ± 2.24
P2	3.02 ± 0.3	8.03 ± 0.7	99.97 ± 2.94
P3	2.41 ± 0.1	7.03 ± 1.6	96.86 ± 3.30
P4	5.01 ± 0.1	15.05 ± 1.1	100.40 ± 1.63
E1	5.90 ± 0.8	16.80 ± 1.3	98.08 ± 0.83
E2	4.70 ± 0.5	11.51 ± 0.7	104.02 ± 2.47
E3	4.82 ± 0.4	9.04 ± 0.2	99.25 ± 2.13
E4	3.09 ± 0.4	23.20 ± 0.6	104.61 ± 0.61
P5	19.71 ± 0.4	49.42 ± 1.6	98.08 ± 0.83
P6	26.82 ± 0.5	53.90 ± 0.08	97.62 ± 0.83
P7	20.71 ± 1.3	39.30 ± 2.7	102.88 ± 2.42
P8	13.60 ± 0.8	54.71 ± 1.9	101.45 ± 0.00
E5	7.60 ± 0.9	36.10 ± 2.5	97.46 ± 0.83

ISSN: 0975-8585

E6	10.15 ± 0.4	26.33 ± 1.5	100.40 ± 3.30
E7	5.51 ± 0.1	15.21 ± 1.1	101.04 ± 0.00
E8	10.00 ± 2.1	47.21 ± 2.9	104.70 ± 0.76
F1	9.82 ± 0.1	22.20 ± 0.2	100.90 ± 0.80
F2	10.00 ± 0.2	25.75 ± 1.1	99.97 ± 2.44
F3	14.51 ± 0.5	31.42 ± 2.4	101.03 ± 2.44
F4	7.10 ± 0.1	19.44 ± 1.7	103.33 ± 1.66
F5	3.20 ± 0.06	19.17 ± 1.3	98.54 ± 2.47
F6	2.20 ± 0.06	18.20 ± 1.4	97.14 ± 0.04
F7	1.80 ± 0.4	15.25 ± 2.7	99.97 ± 2.47
F8	3.00 ± 0.04	23.74 ± 1.9	99.01 ± 2.27
F9	7.29 ± 1.42	11.41 ± 0.18	99.50 ± 1.63
F10	2.82 ± 0.57	6.57 ± 0.2	99.97 ± 2.47
F11	1.55 ±0.5	3.24 ± 0.1	101.40 ± 3.42
F12	0.66 ± 0.20	1.73 ± 0.05	100.00 ± 0.00

Note: values in parenthesis are standard deviation (±SD).

Table 5: Results of stability studies.

Formulation	Disintegration time (sec) (±SD) n=6	Thickness(mm) (±SD) n=6	Drug content (%) ± SD, n=6
P1	14.22 ± 0.22	3.5 ± 0.42	99.97 ± 2.97
P2	12.22 ± 0.37	3.97 ± 0.18	98.08 ± 0.57
P3	9.50 ± 1.25	3.30 ± 0.15	95.55 ± 0.24
P4	2.20 ± 0.12	3.72 ± 0.18	99.01 ± 0.19
E1	42.14 ± 1.50	3.85 ± 0.13	101.5 ± 0.95
E2	37.05 ± 0.85	3.78 ± 0.17	97.14 ± 0.98
E3	25.22 ± 1.00	3.70 ± 0.20	103.3 ± 1.66
E4	36.02 ± 1.42	4.0 ± 0.15	101.4 ± 0.00
P5	22.5 ± 1.50	3.72 ± 0.15	103.3 ± 1.66
P6	552.2 ± 2.50	3.85 ± 0.19	96.6 ± 0.59
P7	845.0 ± 2.48	3.86 ± 0.12	101.5 ± 2.50
P8	375.0 ± 2.98	3.92 ± 0.15	99.97 ± 0.58
E5	57.02 ± 1.85	3.92 ± 0.18	95.55 ± 0.22
E6	45.50 ± 0.52	3.82 ± 0.14	101.5 ± 2.50
E7	42.22 ± 1.50	3.76 ± 0.15	99.97 ± 0.22
E8	64.32 ± 0.58	3.30 ± 0.15	100.40 ± 0 .33
F1	20.50 ± 1.22	3.57 ± 0.18	99.96 ± 0.85
F2	155 ± 2.00	3.92 ± 0.15	98.54 ± 0.53
F3	298 ± 1.50	3.55 ± 0.22	101.3 ± 2.82
F4	20.52 ± 1.25	3.55 ± 0.17	101.3 ± 2.82
F5	37.20 ± 1.52	3.53 ± 0.12	99.91 ± 2.20
F6	27.40 ± 1.29	3.77 ± 0.52	98.08 ± 2.25
F7	22.33 ± 0.36	3.66 ± 0.58	99.01 ± 3.20
F8	42.20 ± 0.57	3.55 ± 0.14	98.52 ± 0.29
F9	19.54 ± 0.29	3.75 ± 0.19	101.4 ± 0.00
F10	11.85 ± 1.00	3.82 ± 0.15	99.82 ± 3.20
F11	9.25 ± 1.27	3.78 ± 0.16	99.82 ± 3.22
F12	5.82 ± 1.20	3.78 ± 0.16	99.97 ± 2.45

Note: values in parenthesis are standard deviation (±SD).

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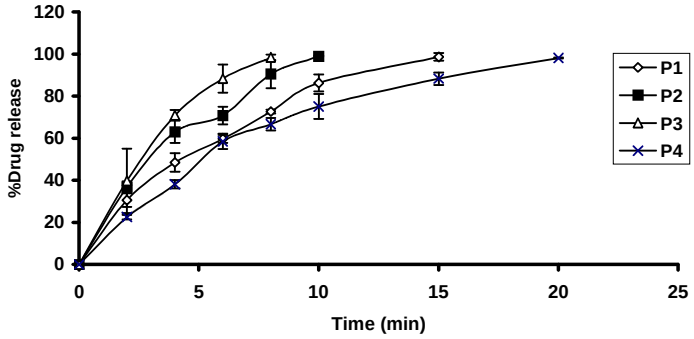

Fig 1: Dissolution profiles of formulations with pvp solid dispersions

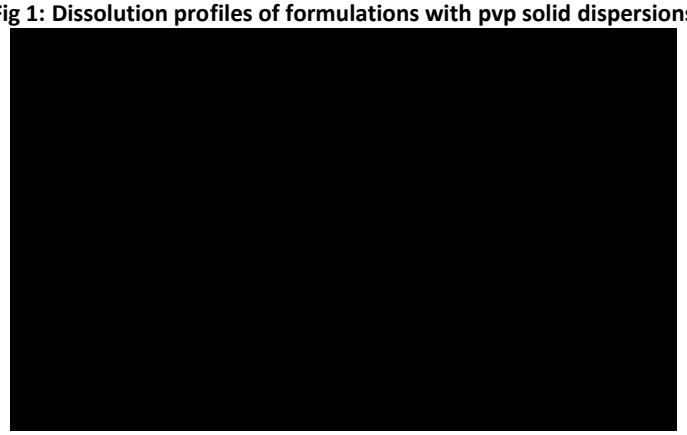

Fig 2: Dissolution profiles formulations with mannitol solid dispersion

Fig 3: Dissolution profiles of formulations with pvp solid dispersion and without superdisintegrant

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Fig 4: dissolution profiles of formulations with mannitol solid dispersion and without superdisintegrant

Fig 5: dissolution profiles of formulations with pvp co-grind method

Fig 6: Dissolution profiles of formulations with mannitol co-grind method

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Fig 7:Dissolution profiles of formulations with different amount of camphor using sublimation method

Fig 8: Dissolution profiles of the best formulations.

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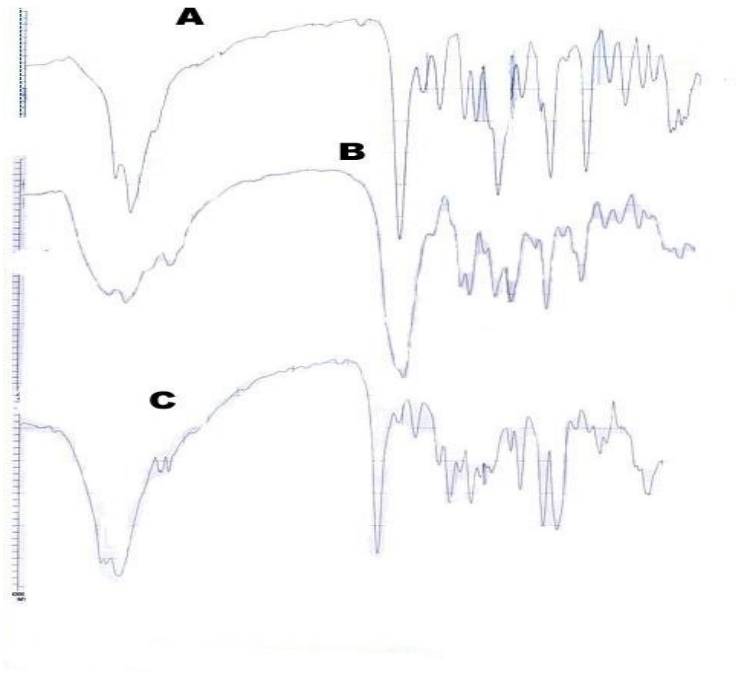

Fig 9: FTIR spectrum of chlorthalidone (A), FTIR spectra P1 (B) and M1(C) of formulations.

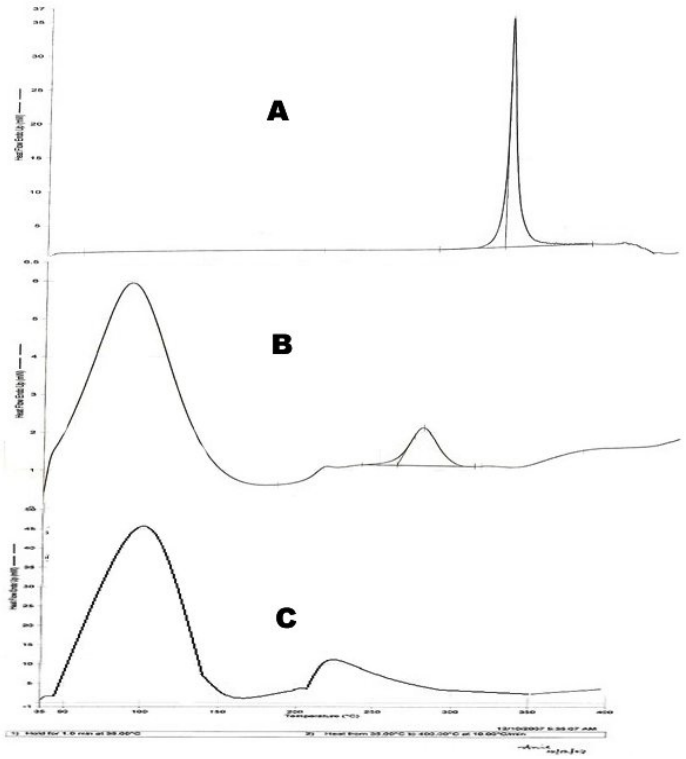

Fig 10: DSC thermogram of pure drug (A), thermogram of solid dispersion with pvp (P3) (B), dsc thermogram of solid dispersion with mannitol (M3) (C).

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