International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.3, No.3, pp 1509-1514, July-Sept 2011

Comparative studies on novel Hydrochlorothiazide- Captopril solid dispersion tablets and commercial tablets

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Abstract: Solid dispersion is a technique which is used to improve the bioavailability of poorly soluble drug by using a water soluble carrier .In this study the freely soluble Captopril drug itself act as drug carrier for poorly soluble hydrochlorthiazide.The tablets of solid dispersions of Hydrochlorothiazide- Captopril were prepared by wet granulation method and characterized by TLC, IR, DSC, X-ray Diffractometry, color, average weight, hardness, friability, disintegration time, drug content, particle size, solubility, dissolution, and stability. The prepared solid dispersion showed the beneficial effects such as improved release, resulting in better bioavailability of hydrochlorothiazide were observed.
Key words: Solid dispersion, Captopril, Hydrochlorothiazide, Dissolution and Bioavailability.

INTRODUCTION

Solid dispersion[1] is one of the approaches followed for improving release behavior of poorly soluble drugs. Researchers so far employed physiologically inert carriers such as PVP, PEG 6000, mannitol, dextrose, xylitol, succinic acid, citric acid....etc. to effect solid dispersions of poorly soluble drugs[2]. An improved release from allopurinol[3], triamterene[4], albendazole[5] solid dispersions has been well documented.In modern clinical practice, combination of drugs has become the law of therapy in many clinical conditions[6]. Hydrochlorothiazide- Captopril, Hydrochlorothiazide-Ramipril, Amiloride HCl- Furosemide are some of combination followed in the treatment of hypertension. On receiving the physicochemical characteristics particularly solubility of drug used in such combinations, surprisingly one of the drugs is found to be insoluble or poorly soluble and the other one soluble. Such a correlation is observed in the combination of hydrochlorothiazide and Captopril. Hydrochlorothiazide is poorly soluble whereas Captopril is freely soluble. This prompted the question whether the poorly soluble hydrochlorothiazide can be solid dispersed in the freely soluble Captopril and whether such a solid dispersion would have beneficial effects such as improved release, resulting in better bioavailability of hydrochlorothiazide. The present study was undertaken to focus on the preparation of tablets containing a novel drug-drug solid dispersion of hydrochlorothiazide and Captopril and to evaluate for its release behavior in comparison to commercial tablets.

MATERIALS

Hydrochlorothiazide (HCT, Courtesy Juharmal and co) Captopril (CAP, Courtesy Medopharm Ltd.), were used as received.
The other reagents were either of pharmacopoeial or reagent grades.

METHIODS

Preparation Of Tablets Containing Hct – Cap Solid Dispersion

HCT-CAP solid dispersion tablets (Tab I and Tab II) were prepared according to the formula given in table (I) by wet granulation method.

Characterisation Studies

The prepared tablets of solid dispersions were characterised by Assay, TLC, IR, DSC, X-ray Diffractometry, Physicochemical characteristics like color, average weight, hardness, friability, disintegration time, drug content, solubility, particle size, dissolution, stability and compared with that of commercial tablets (Table II, III, IV).

Assay

The percentage of the Hydrochlorothiazide and Captopril in the formulations was analysed by UV method at 322nm and at 238nm, 260nm respectively[7].

Thin Layer Chromatography (TLC)

The interaction between the drugs HCT and CAP were evaluated by TLC. The chromatograms of HCT and CAP were carried out by silicagel coated aluminium plates as the stationery phase and CHCL3:CH3OH:NH3 as the mobile phase.The spots of the HCT and CAP were identified by UV at 254nm and iodine vapour method.

IR Spectroscopy (IR)

FT-IR spectrometry was found to be most reliable technique for predicting the possible interaction between the drugs. The IR spectra of solid dispersion tablets and commercial tablets were studied using KBr disc method.

Differential Scanning Calorimetry (DSC)

The physical nature of HCT and CAP were studied using differential scanning calorimetry. The thermogram of all formulations was carried out using Perkin-Elmer DSC equipped with liquid nitrogen at sub ambient accessory. Samples were weighed in an open aluminium pans and scanned at a speed of 20^0c /min.

X-Ray Diffractometry

X-ray diffraction analysis was carried out on formulations using Rigaku miniflex diffractometer.

Physicochemical characteristics

The prepared solid dispersed tablets and commercial tablets were evaluated for various Physicochemical characteristics like color, average weight, hardness, friability, disintegration time, and drug content as per the IP specifications.

Solubility Studies

The effect of Captopril on the solubility characteristics of Hydrochlorothiazide was examined by solubility studies[8].

Particle Size Analysis

The particle size of Hydrochlorothiazide in formulations was analysed using optical microscope.

Dissolutions Studies

Dissolution studies on solid dispersion tablets were performed as per USP method[9]. Tablets of solid dispersion or commercial were added to dissolution medium (1000 ml of 0.1M HCl). 10 ml samples were withdrawn at 10 min intervals of time upto 90 min. The samples were filtered and analysed by UV spectroscopy[7]. Withdrawn samples were replaced by equal volumes of fresh dissolutions medium.

Stability Studies

Stability studies on formulations were performed by sorting at different temperatures 15^0, 32^0, 42^0 and $50^0 \pm 2^0$ C for 60 days. The samples were analyzed for drugs content and release profile.

TABLE I: FORMULATION OF HYDROCHLOROTHIAZIDE- CAPTOPRIL SOLID DISPERSION BY WET GRANULATION

Ingredients	Quantity in mgm/ tablet	
	TAB I	TAB II
Hydrochlorothiazide - Captopril solid dispersion	50	40
Lactose	90	95
Starch	60	65
Avicel	1.5	1.5
Starch paste	8	8
Magnesium Stearate	8	8
Talc	2.5	2.5

RESULTS

Thin Layer Chromatography

The R_f values of Hydrochlorothiazide and Captopril in solid dispersion tablets (TAB I/ COM I) were 0.913 and 0.860 respectively and that in solid dispersion tablets (TAB II/COM II) were 0.909 and 0.845 respectively. The results were comparable with that of pure Hydrochlorothiazide (0.913) and Captopril (0.856), further there was no additional spot observed.

IR

The characteristic peaks of Captopril and Hydrochlorothiazide in solid dispersion tablets (25mg: 25mg and 15mg : 25mg) were observed at the bands 1379.1-1319.4cm^{-1} (N=C stretch), 1601.6-1589.8cm^{-1}(C=O stretch), 676.8cm^{-1} (aliphatic C-H band) for Captopril and 3362cm^{-1} (NH stretch), 1019-1166cm^{-1}(aromatic C=H stretch), 1603cm^{-1}(N=H bend), 1473.3-1461.8cm^{-1} (S=O) stretch for Hydrochlorothiazide and there were found to be identical with that of commercial tablets.

DSC

Pure Captopril produced one endothermic peak at 94.337^0 C whereas pure Hydrochlorothiazide produced two endothermic peaks at 271 341 and 337.53 ^{0}C respectively. Solid dispersion tablets Tab I and Tab II revealed an endothermic peak at 109.004 ^{0}C and 108.670^{0}C respectively. This endothermic peak could be ascribed to the melting of solid dispersions. Further the endothermic peak was absent in both solid dispersions. DSC of commercial tablets was identical with that of pure Hydrochlorothiazide and Captopril.

X-Ray Diffractometry

The presence of numerous distinct peaks in the X-ray diffraction spectra indicates that both the pure drugs, HCT and CAP were present as a crystalline material. The characteristic peaks of HCT appeared at diffraction angle of 2θ at 19, 20, 21.5, 23.5, 25.5 and 39.5^0, with 95%, 100%, 100%, 70% intensity, respectively. Pure Captopril also exhibited diffraction peaks at 2θ at 17, 25.5 and 27.5^0 with 65%, 45%, 45% intensity respectively. Solid dispersion tablets (Tab I and Tab II) showed characteristics peaks 2θ at 19,20,21.5,23.5^0 but with decreased intensity whereas the commercial tablets (com I and com II)were akin to that of pure drugs.

Physicochemical characteristics

The physical characteristics namely color, average weight, hardness and friability and the drugs content of solid dispersion tablets (TAB I and II) were comparable with that of commercial tablets (COM I and II) as recorded in Table II.

Solubility Studies

The solubility of pure Hydrochlorothiazide was found to be 0.2460 mg/ml. The solubility of HCT in 0.001%, 0.0025%, 0.005% and 0.001% of Captopril in dissolution medium was 0.3490, 0.4765, 0.5200 and 0.6125 mg/ml respectively. Thus, Captopril in varying concentrations has significantly increased the solubility of Hydrochlorothiazide in the dissolution medium (Table III).

Particle Size Analysis

The particle size of HCT in solid dispersion tablets was markedly reduced as compared to commercial tablets. The particle size of HCT in tab 1and 11 was about 18.39 µm as compared to that of commercial tablets with 46.44 µm (Table IV).

TABLE II:THE PHYSICO CHEMICAL CHARACTERISTICS OF HYDROCHLOROTHIAZIDE-CAPTOPRIL SOLID DISPERSION TABLETS AND COMMERCIAL TABLETS

S.No	Tablets	Color	Average weight (gm)	Hardness kg/cm^2	Disintegration (min)	Friability (%) w/w	Drug content (%)	
							HCT	CAP
1	TAB-I	Pale White	0.232	4.00	4.10	0.85	98.96	97.94
2	TAB-II	Pale White	0.216	3.37	4.45	0.90	100.51	99.82
3	COM-I	White	0.230	4.00	4.00	0.89	99.19	98.12
4	COM-II	Pale White	0.225	3.82	4.20	0.95	99.30	100.83

TAB I - Tablets of solid dispersion of Hydrochlorothiazide-Captopril (1:1)
TAB II - Tablets of solid dispersion of Hydroclorothiazide-Captopril (1:1.7)
COM I - Commercial tablets
COM II - Commercial tablets

TABLE III: SOLUBILITY STUDIES

S.NO	Concentration of Captopril (%)	Solubility of HCT in mg/ml of solution
1	0.000	0.2460
2	0.001	0.3490
3	0.0025	0.4765
4	0.005	0.5200
5	0.01	0.6125

TABLE IV: PARTICLE SIZE OF HCT IN SOLID DISPERSION TABLETS AND COMMERCIAL TABLETS

S.NO	Formulations	Particle Size (µm)
1	COM I	46.44
2	COM II	46.39
3	TAB I	18.39
4	TAB II	18.65

TABLE V: COMPARISON OF $t_{50\%}$ and $t_{90\%}$ OF DRUG RELEASED FROM SOLID DISPERSION TABLETS AND COMMERCIAL TABLETS

Tablets	Hydrochlorothiazide		Captopril	
	$t_{50\%}$ (min)	$t_{90\%}$ (min)	$t_{50\%}$ (min)	$t_{90\%}$ (min)
TAB I	32	70	27	78
COM I	50	90	28	80
TAB II	30	68	22.5	68.5
COM II	40	89	23.5	70

TAB I = Tablets of Solid dispersion of Hydrochlorothiazide- Captopril (1:1)
COM I = Commercial Tablets
TAB II = Tablets of Solid dispersion of Hydrochlorothiazide- Captopril (1:1.7)
COM II = Commercial Tablets

Dissolution Studies

The release rate of Hydrochlorothiazide was faster from solid dispersion tablets as compared to commercial tablets. The t_{50} and t_{90} of tab I was about 32 min and 70 min respectively as compared to commercial tablets($t_{50\%}$=50.5 min, $t_{90\%}$=>90 min). Similar enhanced rate of release was observed from tab II ($t_{50\%}$=30 min, $t_{90\%}$=68 min) as compared to commercial tablets ($t_{50\%}$=40 min, $t_{90\%}$ =>90 min). Interestingly it was further observed that in the commercial tablets the increase in the carrier (Captopril) concentration was increased the rate of release of Hydrochlorothiazide. The $t_{50\%}$ of HCT was reduced from 50 to 40 min. however there was no change in $t_{90\%}$ which was found to be > 90 min in both cases (Com I, Com II). In contrast, in the solid dispersion tab let under study the rate of release was greatly increased. The $t_{50\%}$ from solid dispersion tablets (Tab I and II) was about 30 min as compared to 50.5 min for com I tablets and 40 min for com II tablets. However, there was no appreciable change in the rate of release of Hydrochlorothiazide due to change in (Captopril) concentration from either Tab I or Tab II wherein $t_{90\%}$ was about 70 min. The release profile of Captopril did not show significant change either in solid dispersion tablets or in the commercial tablets.

Stability Studies

The samples stored at different ambient temperatures did not show significant changes either in the drugs content or in the release profiles of both Hydrochlorothiazide and Captopril.

DISCUSSION

In the present study, a novel drug –drug solid dispersion approach was attempted and investigated for release characteristics. HCT –CAP combination used in hypertension was selected as a model for examining the effect of the novel drug-drug solid dispersion on the release behavior. HCT is poorly soluble and so expected to pose dissolution rate limited

absorption problem whereas CAP being freely soluble is considered devoid of such a problem.

The two different ratios of HCT and CAP namely 25mg:25mg, 15mg:25mg akin to commercial tablets were selected for the preparation by kneading method as a other method fusion and co-precipitation did not yield expected results.

The solid dispersions were compressed into tablets using appropriate excipients as shown in Table (I). The physical characteristics of solid dispersion tablets viz. color, appearance, disintegration ,hardness, friability and drugs content were comparable with that of commercial tablets Table(II). The stability of solid dispersion and commercial tablets was examined through TLC. This was further supported by absence of additional absorption band as evidenced from infra red spectral analysis. The formulations were also found to be stable at different ambient temperature.

The release profile of solid dispersion tablets showed an enhanced rate of release of HCT as compared to commercial tablets (Table V). Further, the solid dispersion tablets did not significantly alter the release characteristics of Captopril which was found to be akin to that of commercial tablets.

The probable mechanisms for increase in the release rate of the drug from solid dispersion tablets were examined. There was a significant reduction in the particle size of HCT in the solid dispersion tablets as compared to commercial tablets as evidenced from microscopic analysis. This has resulted in an increase in the surface area of the drug that would have enhanced the release rate of HCT. The solubility studies showed an increase in the solubility of HCT in Captopril thus proposing micro environmental solubilisation effect on HCT brought about by

Captopril which may be another mechanism for faster rate of release of HCT. Additionally, this mechanism appears to be greatly influenced by the concentration of Captopril as shown in table 3. Change in the crystalline size of HCT is considered another mechanisms for its enhanced rate of release as supported by DSC which showed the shift of two endothermic peaks of HCT at 271 ^{0}C and 341 ^{0}C to 109.004 ^{0}C in the solid dispersion tablets (Tab I) and to 108.670 ^{0}C in the solid dispersion tablets (Tab II). The disappearance of exothermic peak of pure HCT at 335.53 ^{0}C further suggests the reduction in the crystalline nature of HCT that has resulted in increasing the rate of release of HCT. Such an observation was not found in commercial tablets.

The change in crystalline nature of HCT was additionally supported by the observations in the x-ray diffraction analysis that has characteristic peaks of HCT in the solid dispersion tablets were suppressed and also there was a decrease in the height of the diffraction peaks. The possibility of a solid solution formation was also examined by x-ray diffraction analysis. The shift of the position of diffraction lines in Tab I and II as compared to pure HCT supports the contention that the solid dispersion has resulted in the formation of solid solution which would have enhanced the rate of release of HCT from the solid dispersion tablets. Such a mechanism was however not observed with commercial tablets as the diffraction lines were similar to that of pure HCT or CAP.

The results of the release profile of tablets containing solid dispersion propose the hypothesis that the tablets utilizing solid dispersion approach may be beneficial in enhancing the rate of release of poorly soluble drug which is therapeutically advantageous. It may be concluded that this novel drug-drug solid dispersion of HCT-CAP indicates scope foe better therapeutic benefits for HCT through enhanced release rate, absorption, quick dieresis and better anti-hypertensive effect in association with anti-hypertensive drug Captopril. A detailed study on the influence of this novel drug-drug solid dispersion approach on the therapeutic integrity of the formulations will throw more light on its viability in pharmaceutical industries.

Acknowledgement

The authors greatfully acknowledge the facilities provided by IIT, Chennai and Sai Mirra Innopharm, Chennai for completion of this work.

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