International Journal of Pharmacy and Pharmaceutical Sciences
Vol 2, Issue 2, 2010

Research Article

A NOVEL CAPTOPRIL HYDROCHLOROTHIAZIDE SOLID DISPERSION

PADMA PRIYA S[1] *, RAJENDRAN N N[2], LAKSHMI P K[1], UMADEVI S K[1], VAIJAYANTHY V[1], KAUSALYA J[1], RAVICHANDRAN V[1].

[1]Vels College of Pharmacy, Velan Nagar, Pallavaram, Chennai-600 117,Tamilnadu, [2]Madras Medical College, Park town, Chennai-600 003, Tamilnadu
E mail: sppriya11@yahoo.co.in

Received: 10 Dec 2009, Revised and Accepted: 04 Jan 2010

ABSTRACT

The earlier studies reveal that only physiologically inert carriers have been used to effect solid dispersion with improved dissolution of poorly soluble drugs. In the present study, a novel drug – drug solid dispersion approach was applied to prepare solid dispersions in proportions similar to commercial preparations of hydrochlorothiazide and captopril (HCT-CAP) combination. The poorly soluble hydrochlorothiazide was solid dispersed in soluble captopril by kneading method. The solid dispersion was characterised for TLC, spectrophotometric assay, infra-red spectra, DSC and X-ray diffractometry. The influence of captopril on solubility of hydrochlorothiazide was assessed by solubility studies. The solid dispersions were evaluated for *in vitro* dissolution characteristics and the results were compared with that of physical mixtures of HCT-CAP and pure hydrochlorothiazide. The dissolution rate of hydrochlorothiazide from solid dispersions was found to be faster than that of physical mixtures and pure drug. Particle size reduction, micro-environmental solubilisation, change in the crystalline nature of hydrochlorothiazide and formation of solid solution are the probable mechanisms for enhanced dissolution of hydrochlorothiazide.

Keywords : Hydrochlorothiazide, Captopril, Solid dispersion, Dissolution.

INTRODUCTION

Solid dispersion[1] is one of the approaches employed to improve dissolution behaviour of poorly soluble drugs. Physiologically inert carriers[2] have sofar been used to effect solid dispersion of poorly soluble drugs. Solid dispersion with improved dissolution of carbamazepine[3], nimesulide[4], glibenclamide[5] and naproxen[6] has been well documented. While reviewing the literature extensively on this line of research, it was found that only physiologically inert carrier has been employed to produce solid dispersion. In the modern clinical practice combination of drugs is the choice of therapy in many clinical conditions. In many of the combinations followed in the medical practice, surprisingly one of the drugs is found to be insoluble or poorly soluble and the other one soluble. To exemplify this, hydrochlorothiazide captopril combination in which hydrochlorothiazide is poorly soluble and captopril is freely soluble. It is beyond doubt that the poorly soluble hydrochlorothiazide may pose dissolution rate limited absorption problem. In the present study a novel drug-drug solid dispersion approach was applied to prepare solid dispersion of hydrochlorothiazide in captopril in ratios similar to commercial preparations and investigated for its dissolution characteristics and the mechanisms studied.

MATERIALS

Hydrochlorothiazide (HCT) was gifted from M/s. Juharmal co, and Captopril (CAP), was gifted from M/s. Medopharm Ltd. All other reagents were of analytical grade.

METHODS

Preparation of physical mixture

The physical mixtures were prepared by mechanically mixing together, weighed quantities of drugs, captopril and hydrochlorothiazide in ratios (1:1 & 1:1.7) in a mortar, passed through a No.20 sieve and stored in an amber coloured container.

Preparation of solid dispersion

Solid dispersions of HCT-CAP were prepared by kneading method[7]. The drug captopril was melted in a china dish to its melting point. Hydrochlorothiazide was separately dissolved in methanol and the solution was directly added to the melt of the carrier (captopril). The mixture was heated over the water bath to evaporate off the solvent. The residue obtained was dried in a desiccator for two days. The dried material was then passed through N0. 20 sieve and the samples were stored in an amber coloured container.

TLC

The interaction between the drugs HCT-CAP was evaluated by TLC. The chromatogram of HCT-CAP was carried out by silica gel coated aluminium plates as the stationery phase and $CHCl_3$:CH_3 OH: NH3 as the mobile phase. The spots of the HCT-CAP were identified by UV at (254 nm) and Iodine vapour method.

Assay

The percentage of the hydrochlorothiazide and captopril in solid dispersions were analysed by UV method at 238, 260 and 322nm.

IR spectroscopy

FT-IR spectroscopy was found to be the most reliable technique for predicting the possible interaction between the drugs. The IR spectra of all solid dispersions and physical mixtures were studied using KBr disc method.

DSC

The physical nature of Hydrochlorothiazide and captopril were studied using differential scanning calorimetry. The thermogram of HCT-CAP solid dispersions were carried out using perkin – elmer DSC equipped with liquid nitrogen at sub-ambient accessory. Samples were weighed in an open aluminium pans & scanned at a speed of 20^0 c/min.

X-ray diffractometry

X-ray diffraction analysis was carried out on pure hydrochlorothiazide, captopril, physical mixtures and solid dispersions using Rigaku miniflex diffractometer.

Stability studies

Stability studies on all solid dispersions were performed by storing at different temperatures (15^0, 32^0, 40^0 and 50^0C) for 60 days. The sample was analyzed for drugs content and dissolution profile.

Solubility studies

The effect of carrier (Captopril) on the solubility characteristics of hydrochlorothiazide was examined by solubility studies.

Particle size analysis

The particle size of hydrochlorothiazide in all samples was analysed using optical microscope.

Dissolution studies

Dissolution studies on pure drugs, physical mixtures and solid dispersions were performed as per USP method[8]. Samples equivalent to 25 mg or 15 mg of hydrochlorothiazide 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. Sink conditions were maintained by replacing the equal volumes of fresh dissolution medium.

RESULTS

Thin layer chromatography.

The Rf values of hydrochlorothiazide and captopril in solid dispersion (1:1) were 0.913 and 0.860 respectively and that in solid dispersion (1:1.7) 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 (Table 1).

Table 1: TLC of pure drugs, physical mixtures and solid dispersions

S .No.	Formulations	R_f Values	
		Hydrochloro-thiazide	Captopril
1.	Standard Drug	0.913	0.856
2.	Physical Mixtures (1:1)&(1:1.7)		
	HCT - CAP	0.912	0.858
3.	Solid Dispersions (1:1) &(1:1.7)		
	HCT - CAP	0.913	0.860

Drug Content

The percentage of hydrochlorothiazide and captopril were more or less uniform in all physical mixtures and solid dispersions studied and comparable with that of pure drugs (Table 2).

Table 2: Estimation of drug content in solid dispersions

Error! Bookmark not defined.S .No.	Formulations		Amount of Drug (mg)	Percentage of Drug (%)
1.	SDK_1			
		HCT	25.31	101.25
		CAP	24.84	99.36
2.	SDK_2			
		HCT	15.04	100.28
		CAP	25.47	101.87

IR

The characteristics peaks of captopril and hydrochlorothiazide in both physical mixtures and solid dispersions (1:1 & 1:1:7) were observed at the bands 1379.1 – 1319.4 cm^{-1} (NC stretch) 1601.6 – 1589.8 cm^{-1} (C=0 stretch) 676.8 cm^{-1} (aliphatic C-H band) for captopril and 3362^{-1} (NH stretch), 1019-1166cm^{-1} (aromatic CH stretch), 1603 cm^{-1} (NH bend) 1473.3 – 1461.8 cm^{-1} (S=0) stretch for HCT which were found to be identical with that of pure samples.

DSC

Pure captopril produced one endothermic peak at 94.337^{0}C. Pure hydrochlorothiazide produced two endothermic peaks and one exothermic peak at 271^0, 341^0 and 337.53^{0}C respectively. Solid dispersions (1:1 and 1:1.7) 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 exothermic peak was missing in both solid dispersions.

X-ray diffractometry

The presence of numerous distinct peaks in the X-ray diffraction spectra indicates that both the pure drugs, HCT-CAP are present as a crystalline material. The characteristics peaks of pure HCT that appeared at diffraction angle of 2θ were at 19^0, 20^0, 21.5^0, 23.5^0 , 25.5^0, 39.5^0, with 95% ,100%, 100%, 70% intensity, respectively, pure captopril also exhibited a diffraction peaks at 2θ at 17^0, 25.5^0 & 27.5^0 with 65%, 45%, 45% of intensity respectively. Solid dispersions showed characteristic peaks at 2θ of 19, 20^0, 21.5^0, 23.5^0 similar to that observed with pure drugs.

Stability studies

The samples stored at different ambient temperatures did not show significant changes in the drugs content & dissolution profiles of both hydrochlorothiazide and captopril.

Solubility studies

The solubility of pure hydrochlorothiazide was found to be 0.2460mg/ml. The solubility of HCT in 0.001%, 0.0025%, 0.005% and 0.01% 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.

Particle size analysis

The particle size of HCT in captopril was markedly reduced as compared to pure HCT. The particle size of HCT was reduced from 54.54 μm to 12.48 and 12.65 μm in HCT –CAP solid dispersions 1:1 & 1:1:7 respectively (Table 3).

Table 3: Particle size of pure hydrochlorothiazide and its solid dispersions with captopril.

S .No.	Samples	Particle Size (μm)
1.	Pure Hydrochlorothiazide	54.52
2.	*SDK_1	12.48
3.	**SDK_2	12.65

*SDK_1-Hydrochlorothiazide–Captopril (1:1);

**SDK_2-hdrochlorothiazide – Captopril (1:1.7)

Dissolution studies

Solid dispersions of HCT with captopril showed enhanced rate of dissolutionas compared to pure drug and physical mixtures. The $t_{50\%}$ & $t_{90\%}$ HCT in HCT – CAP solid dispersions (1:1) were 13.5 min, 35 min respectively. The rate of dissolution was much better than the PM in which $t_{50\%}$ & $t_{90\%}$ were 40 min and >90 min respectively. The t50% and t90% of HCT in HCT – CAP solid dispersions (1:1.7) were 12 min & 29 min respectively as compared to physical mixture which showed $t_{50\%}$ at 32.5 min & $t_{90\%}$ at > 90 min respectively. Both physical mixtures & solid dispersions of HCT – CAP of both ratios produced enhanced rate of dissolution when compared with pure hydrochlorothiazide ($t_{50\%}$ = 47.5min; $t_{90\%}$ = > 90 min. Further, the dissolution profile of captopril from the solid dispersions was akin to that of physical mixtures and pure drug shown in Figure 1.

DISCSSION

Earlier studies reveal that researchers adopted solid dispersion approach by employing physiologically inert carriers in order to improve dissolution of poorly soluble drugs. In the present study a novel drug-drug solid dispersion approach was attempted and investigated for dissolution characteristics. In the modern clinical practice combination of drugs has become the rule of therapy. Surprisingly, in many of such combinations of drugs one of the drugs is found to be soluble & the other one insoluble or poorly soluble. The relevant question now is what happens when the poorly soluble drug is solid dispersed in soluble drug that is used in combination. In this study, HCT-CAP combination used in hypertension was chosen as a model for investigating the possibility of the novel drug-drug

solid dispersion approach. HCT being poorly soluble may pose dissolution rate limited absorption problem and captopril being feely soluble may not pose such a problem.

HCT was solid dispersed in captopril in different ratios 1:1 & 1:1.7 similar to proportions available commercially. The solid dispersions were affected by kneading method as discussed earlier as other methods namely fusion & co-precipitation did not yield expected results. The stability of solid dispersions was confirmed by TLC and spectrophotometric assay. Infra-red spectral analysis indicated absence of chemical interaction between HCT and CAP as shown in Fig, (1-4) thus further supporting the stability of solid dispersions. The dissolution studies showed an enhanced rate of dissolution of HCT from solid dispersions as compared to that of physical mixtures (Fig. 14 & 15) and pure drugs. The dissolution rate of CAP remained unchanged or stable either in the solid dispersions or in the physical mixtures and the results was comparable with that of pure captopril.

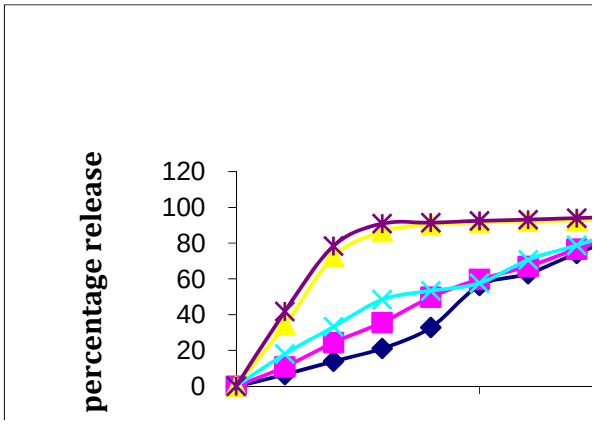

Fig. 1: *In vitro* release of HCT in pure drug, physical mixture and solid dispersion

The following mechanism can be proposed for an enhanced rate of dissolution of HCT from all the samples investigated. The particle of size of HCT was greatly reduced in the solid dispersions as compared to pure drugs as supported by microscopic analysis. (Table 3) As a result, an increase in the surface area effected by particle size reduction might be one of the mechanisms contributing to an increased rate of dissolution of HCT. Another mechanism that can be proposed for an enhanced dissolution of HCT is the micro environmental solubilisation of the drug brought about by the water soluble drug, captopril as evidenced from the solubility studies (Table 2). Interestingly the effect of micro environmental solubilisation of HCT by CAP appears to increase as the concentration of CAP was increased. The results of the differential scanning calorimetry further explored the mechanisms of enhanced dissolution. There was a change in the crystalline size of HCT as supported by the shift of two endothermic peaks of HCT at 271^0C and 341^0C to 109.004^0C in the solid dispersions of 1:1 ratio and to 108.670^0C in the solid dispersions of 1:1.7 ratios. Additionally, the disappearance of exothermic peak of pure HCT at 337.53^0C further supports the view that enhanced dissolution of HCT is due to change in the crystalline nature of HCT. An insight into the mechanism for enhanced dissolution of HCT was further examined by X-ray diffraction analysis. The suppression of the characteristic peaks of HCT in the solid dispersion and decrease in the height of the diffraction peaks propose the reduction of crystalline size of HCT that has resulted in increasing the rate of dissolution of HCT from solid dispersions. Interestingly, the possibility of the formation of solid solution was evidenced by the shift of the position of the diffraction lines as compared to pure HCT and the solid solution formation is the other mechanism that enhance the rate of dissolution of HCT from the solid dispersions

The present novel drug – drug solid dispersion approach proposes the view that wherever a poorly soluble drug is combined with the soluble drug in the therapy of clinical disorders, the soluble drugs can play the role of physiologically inert carriers to effect solid dispersion for enhanced dissolution and absorption of poorly soluble drugs. This gives a signal to extending this approach to similar combinations of drugs used in clinical practice so as to improve bioavailability of poorly soluble drugs through improved dissolution.

REFERENCES

1. Taneja L N Khopade A J Jain M K Indian drugs (1997) 34(2) 72-77
2. Chiou WL and Riegelman SJ J Pharm sci (1971) 60 1283-97
3. Ruckmani P and Munnira. Eastern Pharmacist (1999) 12(2) 117-119
4. Chowdri KPR Suseela devi Y Deepika M Eastern Pharmacist (1999) 41(2) 105 – 107
5. Panagopoulou A and Maramataris S Int.J.Pharm (1999) 195 (11) 239-246
6. Hirasawa N Danja K Haruna M Otuska A. Chemical and Pharmaceutical Bulletin (1998) 46 (6) 1027-1030
7. Chiou WL and Riegelman SJ J Pharma Sci (1971) 60 1283 – 1297
8. United States of Pharmacopoea, USP 23/NFI8 Mack Publishing Co Eastern (1995) 2896-97 2620.