INTRODUCTION
Solid dispersion is one of the approaches employed to improve dissolution behaviour of poorly soluble drugs. Physiologically inert carriers have so far been used to effect solid dispersion of poorly soluble drugs. Solid dispersion with improved dissolution of carbamazepine, nimesulide, glibenclamide and naproxen has been well documented. While reviewing the literature extensively on this line of research, it was found that only physiologically inert carriers have 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 limitation 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 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.

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 & 1:1.5) in a mortar, passed through No.20 sieve and stored in an amber coloured container.

Preparation of solid dispersion
Solid dispersions of HCT-CAP were prepared by kneading method. 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 No. 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 CHCl₃:CH₃OH: NHS 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 322 nm.

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 20⁰c/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 (15⁰C, 32⁰C, 40⁰C and 50⁰C) 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 analyzed using an optical microscope.

Dissolution studies
Dissolution studies on pure drugs, physical mixtures and solid dispersions were performed as per USP methods. 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 up to 90 min. The samples were filtered and analyzed 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

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Formulations</th>
<th>Rf Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td>1.</td>
<td>Standard Drug</td>
<td>0.913</td>
</tr>
<tr>
<td>2.</td>
<td>Physical Mixtures (1:1)&amp;(1:1.7)</td>
<td>0.912</td>
</tr>
<tr>
<td></td>
<td>HCT - CAP</td>
<td>0.913</td>
</tr>
<tr>
<td>3.</td>
<td>Solid Dispersions (1:1)&amp;(1:1.7)</td>
<td>0.913</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Error! Bookmark not defined.S</th>
<th>Formulations</th>
<th>Amount of Drug (mg)</th>
<th>Percentage of Drug (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>SDK1</td>
<td>HCT 25.31</td>
<td>101.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAP 24.84</td>
<td>99.36</td>
</tr>
<tr>
<td>2.</td>
<td>SDK2</td>
<td>HCT 15.04</td>
<td>100.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAP 25.47</td>
<td>101.87</td>
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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 2θwere at 19°, 20°, 21.5°, 23.5°, 25.5°, 39.5° with 95%, 100%, 100%, 70% intensity, respectively, pure captopril also exhibited a diffraction peaks at 2θat 17°, 25.5° & 27.5° with 65%, 45%, 45% of intensity respectively. Solid dispersions showed characteristic peaks at 2θ of 19, 20°, 21.5°, 23.5° similar to that observed with pure drugs.

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

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 0.01% 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.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Samples</th>
<th>Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pure Hydrochlorothiazide</td>
<td>54.52</td>
</tr>
<tr>
<td>2.</td>
<td>SDK1</td>
<td>12.48</td>
</tr>
<tr>
<td>3.</td>
<td>**SDK2</td>
<td>12.65</td>
</tr>
</tbody>
</table>

*SDK1-Hydrochlorothiazide-Captopril (1:1);

**SDK2-hydrochlorothiazide – Captopril (1:1.7)

Dissolution studies
Solid dispersions of HCT with captopril showed enhanced rate of dissolution compared to pure drug and physical mixtures. The t50% 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 t50% & t90% were 40 min & >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 t50% at 32.5 min & t90% 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 (t50% = 47.5 min; t90% = > 90 min). Further, the dissolution profile of captopril from the solid dispersions was akin to that of solid dispersions and pure drug shown in Figure 1.

DISCUSSION
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 freely 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](image)

The following mechanism can be proposed for an enhanced rate of dissolution of HCT from all the samples investigated. The particle 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°C and 341°C to 109.00°C in the solid dispersions of 1:1 ratio and to 108.67°C in the solid dispersions of 1:1.7 ratios. Additionally, the disappearance of exothermic peak of pure HCT at 337.5°C 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