SUMMARY AND CONCLUSIONS

Summary:

The therapeutic efficacy of a drug product intended to be administered by the oral route depends on its absorption by the gastro – intestinal tract. It is well established that dissolution is frequently the rate-limiting step in the gastro intestinal absorption of a drug from a solid dosage form. Poorly soluble drugs have been shown to be unpredictable and are slowly absorbed as compared with drugs with higher solubility. Consequently, these drugs present great challenges to further development into bioavailable dosage forms. Hence it is important to enhance the aqueous solubility, dissolution rate and bioavailability of these drugs from its oral solid dosage forms. Solid dispersion technique and modified starches like oxidized potato starch and gelatinized oxidized potato starch have been used to improve the dissolution properties and bioavailability of poorly water-soluble drugs. This study has demonstrated the possibility of markedly improving the dissolution performance of nimodipine by solid dispersion technique with gelatinized oxidized potato starch and oxidized potato starch.

Nimodipine has been used in the treatment of hypertension. The major drawback in the therapeutic application and efficacy of nimodipine as oral dosage form was its very low aqueous solubility because of its hydrophobic nature. Therefore, a favorable formulation which can enhance solubility and dissolution rate of this model drug may help effectively in the therapeutic area of hypertension and treatment. Thus, studies were carried out to improve the solubility and hence dissolution rate, efficiency and bioavailability of poorly soluble drug nimodipine through solid dispersion technique using gelatinized oxidized potato starch and oxidized potato starch as a novel carrier.

The brief introduction about bioavailability of dosage forms were given in chapter –1. Further more, in this chapter introduction on dissolution rate and various approaches to improve the solubility, particularly on solid dispersion technology was elaborated. In addition, this chapter discussed about modified starches and their pharmaceutical applications. The aim and objective was discussed in chapter-2. Chapter -3 deals with the literature review which included an overview on nimodipine and out
lined their usage, contraindication and side effects. Literature survey related to preparation and past research work on oxidized potato starch, gelatinized oxidized potato starch and potato starch were also included in the chapter.

**Chapter -4** the plan of investigations of the present study were discussed.

**Chapter -5** discussed about materials used, analytical and experimental methods employed in the present investigation. The first part of this chapter described preparation of modified starches like oxidized potato starch and gelatinized oxidized potato starch by reported methods and characterized by DSC, FT-IR, XRD and SEM. The later part of this chapter described in detail about method of preparation of physical mixtures and solid dispersions of nimodipine with OPS and GOPS. Solid dispersions of nimodipine were prepared with modified starches in seven different ratios of drug and carrier (1:1, 1:3, 1:9, 1:19, 2:1, 4:1 and 8:1 W/W) by solvent evaporation method. The preceding part of this chapter dealt with the methods of characterization of SDs in solution and solid state. Characterization in solution state was made by drug content uniformity and *in vitro* dissolution studies. Characterization in solid state was done by various analytical techniques such as FT-IR, XRD, DSC and SEM studies. The last part of this chapter covered the preparation tablets and hard gelatin capsules of solid dispersions and their evaluation studies.

**Chapter -6** summarized and discussed all the research results of SDs as well as physical mixtures and pharmaceutical dosage form such as tablets and capsules according to our plan of investigations as described in **chapter-4**.

All the research results of SDs, physical mixtures and pharmaceutical dosage forms were discussed in detail in **chapter -7**. The first section of this chapter i.e., 6.1, 6.2, 6.3, discussed about research results of modified starches (OPS and GOPS) where as 6.4 discusses about calibration and characterization of pure drug nimodipine, 6.5 and 6.6 discussed about research results of SDs and physical mixtures, 6.7 and 6.8 discussed about the results of pharmaceutical dosage forms such as tablets and capsules formulated employing SDs and physical mixtures of potato starch and modified starches (OPS and GOPS)
The modified starches (OPS and GOPS) prepared were found relatively non hygroscopic when compare to potato starch. The percentage of moisture absorbed was less than 8.3%.

The modified starches (OPS and GOPS) prepared were found free flowing based on their angle of repose and compresibility values shown in table 6.3, the decomposition temperature of PS, OPS and GOPS were 146° C, 165° C, 220° C and 208° C. The swelling index of PS, OPS and GOPS are 0.2, 1.0, 6.5 and the high swelling index of GOPS indicated disintegrant property. All the modified starches passed the starch identification tests by producing reddish-violet color when treated with iodine test solution.

The particle size distribution in PS and modified starches showed that in order of GOPS> OPS>PS.

The FTIR spectra of all modified starches (OPS and GOPS) prepared were compared with native potato starch. The bands of OPS and GOPS shown above 1022 cm\(^{-1}\) as 1136.4 cm\(^{-1}\). The presence of peaks confirmed the formation of modified starches from native potato starch.

The DSC thermograms of modified starches were compared with native potato starch. The prepared modified starches exhibited little shift in thermograms. The OPS exhibited an exothermic peak at 147.22° C where as GOPS exhibited endothermic peak of 90.90° C, with significant change in the heat flow. This change in heat flow indicated the change in crystallinity of modified starches compared to PS which is at 111.20° C. The XRD data of modified starches were compared to native potato starch, low intensity peaks in modified starch indicated decrease in crystallinity of prepared OPS and GOPS.

Morphological features of modified starches and potato starch were examined by SEM analysis. A change of its original morphology, size and shape of modified starches OPS and GOPS were observed. The SEM pictures of prepared modified starches revealed the formation of large masses of undifferentiated particles in GOPS which were different from their of OPS and native potato starch.
All nimodipine physical mixtures prepared were found to free flowing. The percent drug content was estimated to confirm that there was no degradation of drug and expected amount of drug was present in obtained product. Low RSD values in the drug content of physical mixtures indicated uniform drug distribution in all prepared batches (1:1, 1:3, 1:9, 1:19, 2:1, 4:1 and 8:1). The spectral characterization of NM-modified starches (2:1) physical mixtures were studied FT-IR, XRD, DSC and SEM. The physical mixtures were found to be stable after three months stability studies conducted at 40°C.

All SDs prepared were found free flowing. The percentage drug content and yield were estimated to confirm that there was no degradation of drug and expected amount of drug was present in obtained product. Low percent relative standard deviation (%RSD) values in the drug content of SDs indicated uniform drug distribution in all prepared batches, FTIR spectra of all SDs prepared were compared with the corresponding PMs as well as pure drug alone. The FT-IR studies of SDs suggested the possibility of intermolecular hydrogen bonding between amide of nimodipine and hydroxyl groups of the carriers. DSC thermograms of nimodipine were compared with NM-modified starches SDs and PMs prepared by different method. SDs prepared at all ratios exhibited shift of endothermic peak of nimodipine were significant and change in intensity as well as enthalpy values in the heat flow. This change in heat flow indicated the change in a crystallinity of drug and attesting a decrease in crystallinity or partial change in crystal form of drug in SDs.

The powder XRD studies of nimodipine solid dispersion revealed that the crystallinity of nimodipine was significantly reduced, evidenced by marked decrease in intensity of peaks. The XRD results of all solid dispersion systems suggested that no alteration in the crystal structure of nimodipine, but the crystallinity being modified and reduced to a considerable extent. The FT-IR and DSC studies also supported the same hypothesis which was confirmed by the XRD results.

Morphological features of the nimodipine solid dispersions prepared were examined by SEM analysis. A change in the original morphology, size and shape of nimodipine-modified starches were observed in SDs, the SEM photographs of all SDs
revealed the formations of large masses of undifferentiated particles, which were different from those of raw materials.

The in vitro dissolution rate tests were used to characterise the NM-modified starches. The in vitro dissolution studies of pure nimodipine, PMs and SDs were carried out in 900ml of 0.1 N HCl using 10% methanol on USP XXI type –II dissolution rate test apparatus. The release of nimodipine from PMs and SDs were measured spectrophotometrically at 358 nm. The dissolution rate of nimodipine was significantly improved after preparing its SDs system employing GOPS compared to PS, OPS and nimodipine alone. Higher dissolution rates and dissolution efficiency of nimodipine from GOPS was in accordance with its hydrophilic nature.

The DE$_{30}$ values of the SDs prepared by employing GOPS at 1:9 were relatively high when compared with OPS and PS. The DE$_{30}$ values of SDs were high when compared to PMs and nimodipine alone the overall rank order of dissolution efficiency of various formulations was

\[ \text{NM-GOPS} > \text{NM-OPS} > \text{NM-PS} \]

\[ \text{SD} > \text{PM} > \text{Pure nimodipine} \]

Dissolution profile of all solid dispersion systems were analysed with kinetic models. The release of drug from the preparation followed first order (best fit model).

The tablets and hard gelatin capsules were formulated employing PMs and SDs of all modified starches (OPS and GOPS) and native potato starch. The resultant tablets and capsules were evaluated for pharmacopoeial and non-pharmacopoeial tests. The release profile of NM tablets were compared with commercial tablet (nimodip 30mg). The dissolution rate of tablets containing SDs of GOPS was high compared to nimodipine commercial tablets (nimodip 30mg). Higher dissolution rate and dissolution efficiency of formulated nimodipine tablets and capsules from SDs was in due to molecular dispersion of NM in GOPS.
CONCLUSIONS

Modified starches such as oxidized potato starch and gelatinized oxidized potato starch were successfully prepared by reported methods and characterized. Solid dispersions and physical mixtures of nimodipine with modified starches were successfully prepared and evaluated. The nimodipine SDs and PMs were formulated successfully into pharmaceutical dosage forms such as tablets and capsules. The following conclusions were drawn from the present investigations.

- The high swelling index of GOPS indicated its good disintegration property
- The FT=IR spectra of OPS and GOPS indicates the decrease in crystallinity by increase in bands above 1022 cm\(^{-1}\) which was supported by XRD by revealing low intense peaks and DSC exhibited little shift in thermograms SEM photographs shown large irregular masses of undifferentiated particles in GOPS which poses good drug carrying capacity
- All SDs and PMs prepared were found free flowing and low RSD values in percent drug content estimation indicated uniform drug distribution in all prepared batches.
- The FT-IR studies of SDs with modified starches indicated that there was no interaction between NM and carriers.
- DSC studies of SDs with modified starches demonstrated the decrease in melting enthalpy (AH) values in 1:9 and 2:1 prepared batches indicted decrease in crystallinity and change in crystal form of drug.
- The XRD results of SDs suggested that decrease in crystallinity of NM
- All SEM pictures of SDs revealed that interaction was not observed between drug and carrier in the solid state and were in accordance with the results obtained from FT-IR, XRD and DSC studies
- The dissolution rate of nimodipine was significantly improved after preparing its SDs with GOPS compared to nimodipine alone.
- The DE\(_{30}\) values of SDs prepared by solvent evaporation method were relatively high compared to the values from the PMs and nimodipine alone
Drug dissolution in SDs was higher in GOPS compared to OPS and PS. The drug dissolution in SDs was higher in 1:19 and 1:9 compared to 2:1, 4:1 and 8:1. The overall rank order of improvement in dissolution properties of nimodipine were found in the following order,

\[
\text{SD} > \text{PM} > \text{GOPS} > \text{OPS} > \text{PS}
\]

\[
1:19 > 1:9 > 1:3 > 1:1 > 2:1 > 4:1 > 8:1
\]

- The DE$_{30}$ values of SDs prepared with GOPS were higher than those prepared by other modified starches.
- The dissolution rate of formulated nimodipine tablets employing SDs of NM-GOPS was significantly improved when compared to commercial tablet (nimodip 30). All other evaluation parameters of tablets were found to be satisfactory based on their evaluation test reports.
- The dissolution rate of formulated nimodipine capsules employing SDs of NM-GOPS was significantly improved. When compared to commercial capsule nimodip 30mg. The overall rank order of dissolution rate of nimodipine from formulated pharmaceutical dosage form and commercial formulation was

\[
\text{SDs tablets} > \text{SDs capsules} > \text{commercial tablet nimodip 30mg}
\]

With the use of GOPS, the dissolution rate of poorly water soluble drug NM has increased 5 fold in solid dispersions. By considering results, it can be concluded that, from the two modified starches. GOPS was found to be compatible with drug and also posses high swelling property, it was given good drug carring capacity. So far the OPS and GOPS were limited to paper industry, polymer industry. The results of present investigation support that the GOPS can also be used as a pharmaceutical excipient in preparation of pharmaceutical dosage forms like tablets and capsules etc.