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PREPARATION AND CHARACTERIZATION OF TURNERY INCLUSION COMPLEX OF NAPROXEN B-CYCLODEXTRIN AND POLYMER NUSLIN. (RESEARCH ARTICLE)

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ABSTRACT
Naproxen suffers from poor solubility and thereby poor absorption, which ultimately leads to poor bioavailability. In present study, an attempt has been made to formulate and characterize Naproxen complex, using β-CD and polymer in order to enhance its solubility and dissolution rate. Phase solubility study was used to investigate the interaction of the drug in binary system as well as ternary system. It was observed that solubilization of Naproxen by β-CD was further enhanced by using Leucine. Several methods were used to prepare ternary complex of Naproxen – β-CD – Leucine. Ternary complex prepared by co-evapouration method containing Naproxen – β-CD – Leucine has shown the fastest dissolution rate as compared to pure Naproxen as well other methods were used to prepare complexes. The prepared ternary complex system was characterized by ction studies. Differential scanning calorimetry and scanning electron microscopy. It was observed that enhancement in solubility as well as dissolution rate of Naproxen was due to formation of ternary complex system.

KEYWORDS:

Literature review

- **Pinackin Pandya,** Narendra **Kumar Pandey** have reported the formulation and haracterizationn of ternary complex of poorly soluble duloxetine hydrochloride.
- **Mallikarun Rao N et al.** in 2011 have reported the simultaneous estmation of S(-) Amlodipine and Hydrochlorothiazide in bulk and tablet dosge form y simultaneous equation method by U.V. spectrophotometry t 239nm, 271nm. The recovery of the Amlodipine and Hydrochorthiazide were foun ear to 100%. The results were found to satisfactory and reproducible.

NEED OF WORK
To enhance the aqueous solubility of Naproxen by using cyclodextrin in presence or absence of auxiliary substance.

To investigate its effect on their physicochemical characteristics.

AIM & OBJECTIVES
To prepare inclusion complexes of Naproxen by using various methods such as kneading etc.

To study the phase solubility and stability constant for the complex.

To study In vitro drug release.

To characterised the complex formations by techniques such as Fourier transformation infrared spectroscopy (FTIR).

INTRODUCTION
Naproxen is a propionic acid derivatives and a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activities. The chemical name for naproxen is (S)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid. Its molecular formula is C14H14O3 having molecular weight 230.26 g/mole. Naproxen is an odourless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high ph. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8. The elimination half life of naproxen ranges from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life. It has the following structure:

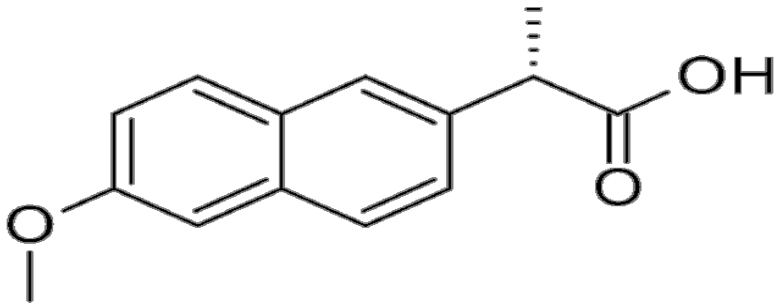


Fig. 1: Chemical structure of Naproxen.

Nproxen tablet are available as white tablets containing 250 mg, 375 mg and 500 mg of naproxen for oral administration. The inactive ingredients are croscarmellose sodium, providone and magnesium stearate. With a pka of 4.15, it is readily absorbed in the GI tract and has a bioavailability of 95%. Naproxen inhibits the activity of the enzymes cyclo-oxygenase 1 and 2, resulting in a decreased formation of precursors of prostaglandins and thromboxanes. The resulting decrease in prostaglandin synthesis is responsible for the therapeutic effect of naproxen. Nproxen also causes a decrease in the formation of thromboxane A2 synthesis, by thromboxane synthase, thereby inhibiting platelet aggregation. After administration of naproxen tablets, peak plasma levels are attained in 2 to 4 hours. Nproxen has a volume of distribution of 0.16L/Kg. At therapeutic levels naproxen is greater than 99% albumin-bound.Naproxen is extensively metabolized in the liver to 6-o-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-o-dessssmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites. The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (<1%) or their conjugates (66% to 92%). The plasma half life of naproxen anion in humans ranges from 12 to 17 hours.

DRUG PROFILE
NAPROXEN

Naproxen is a nonsteroidal anti –inflammatory drug (NSAID) advocated for use in painful and inflammatory rheumatic and certain nonrheumatic conditions. It may be sdministered orally or rectally using a convenient once or twice daily regimen. Dosage adjustments are not usually required in the elderly or those with mild renal or hepatic impairment although it is probably prudent to start treatment at a low dosage and titrate upwards in such groups of patients. The drug is effective in many rheumatic diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and nonarticular rheumatism, in acute traumatic injury, and in the treatment of and prophylaxis against acute pain such as migraine, tension headache, postoperative pain, postpartum pain and pain associated with a varity of gynaecological procedures. The adverse effect profile of naproxen is well established, particularly compared with that of many newer NSAIDs, and the drugs id well tolerated. The naproxen considered as a first line treatment for rheumatic disease and various pain states.

Structure

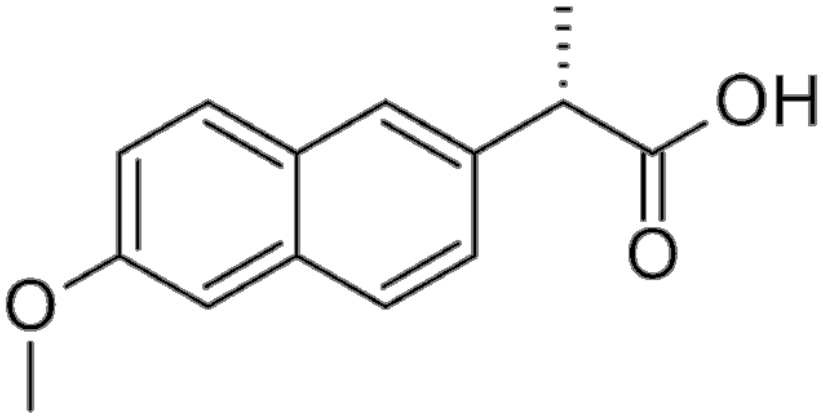


Fig. 2: Chemical structure of Naproxen.

Chemical name: (s)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid.
Molecular formula: C14H14O3
Molecular weight: 230.26

Physical mixture: Naproxen occurs as a white to off-white crystalline powder
Solubility: Naproxen soluble in solvents such as DMSO, ethanol, and dimethyl formamide.

Categories:
*Anti-Inflammatory agents, Non-steroidal
*Cyclooxygenase Inhibitors
*Gout suppressants
Melting point: 152-155

Biotransformation / Drug metabolism: Naproxen is extensively metabolized to 6- 0-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes.

Absorption: Naproxen itself is rapidly and completely absorbed from the GItract with an in vivo bioavailability of 95%.

Pharmacodynamics: Naproxen is a nonsteriodal anti-inflammatory drug with analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics: Naproxen is rapidly and completely absorbed from the gastroinsestinal tract with an in vivo bioavailability of 95%. The elimination half life of naproxen ranges from 12 to 17 hours. Steady state levels of naproxen are reached in 4 to 5 days and degree of naproxen accumulation is consistent with this halh-life.

Mechanism of action: The mechanism of action of naproxen, like that of other NSAIDs, is believed to be associared with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity.

Adverse effect: The most common adverse reaction are gastrointestinal pains (heartburn, abdominal pain, nausea, constipation, all occurs more than 5% of treated subjects). Central nervous problems such as headache, somnolence, tinnitus, vertigo, as well as edemas and respiratory problems, are not uncommon either. Skin rashes, pruritus, diarrhea, insomnia, depressions, myalgias etc. are not observed very frequently with naproxen. Dangerous side effects (gastrointestinal bleeding or perforation, acute interstitial nephritis, hepatitis, blood production disorders) are rare.

LITERATURE REVIEW

- **Pinackin Pandya,** Narendra **Kumar Pandey** have reported the formulation and haracterizationn of ternary complex of poorly soluble duloxetine hydrochloride.
- **Mallikarun Rao N et al.** in 2011 have reported the simultaneous estmation of S(-) Amlodipine and Hydrochlorothiazide in bulk and tablet dosge form y simultaneous equation method by U.V. spectrophotometry t 239nm, 271nm. The recovery of the Amlodipine and Hydrochorthiazide were foun ear to 100%. The results were found to satisfactory and reproducible.
- **Khan. Rizwan et al. in** 2012 RP HPLC method has been developed for te simultaneous deterinatio of Losartan Potassium and Hydrochorothiazide from combined dosage form by reverse phase C18 coloum. The sample was analysed using Triethlylaminne: Acetonitrile: Methanol in the ratio of 33:27:40 as a mobile phase at a flow rate of 1.0ml/min and detection at 270nm.
- **Maria Arlete et al.** in 2011 havve reported the development off Hydrochlorothiazide β- CD pharmaceutical composition in order to improve water solubility and bioavilability of the drug. The HTZ:β-CD complexes were prepared by three different methods: spray drying, freez drying and fluid bed. Complexes were characterized by thermal analysis, Fourier transfor infrared sperctroscopy, powder X-ray diffractometry, NMR, SCM, particle analyss and intrinsic dissolution. Increased diuretic effect was observed to HTZ: β- CD obtained by fluid bed in comparison to free drug in rats.
- **Ahmad M. O. et al.** 1996 have reported Hydrochlorothiazide and Bendrofuazide Complexes with β-CD in aqueous solution in solid state as studied by solubility method, NMR, XRPD, DSC. Al type phase solubilty curved obtained indicating the formation of 1:1 inclusion.
- **R. M. Martins et al.** 2011 carried out study the prepafratin of microcapsule of hydrochlorothiazide, containing polyvinylpyrrolidone and colidal silicon dioxide by spray drying. The experiments followed a Box-Behnken design to evaluate a influence of the atomization pressure, drug content and outlet temperature on the process yield ad moisture content. Photomicrographs by SEM were obtained.
- **Rashmi V. Trivedi et al.** in 2011 investigation used novel method by employing losartan potassium as carrier for solid dispersion of HTC as well as both losartan potassium and inert carrier urea in combination for solid dispersion of HCT. Both the solid dispersion were prepared by physical mixture, paste method, solvet evaporation metod nad fusion method. Out of this solvent method exhibited maximum solubility. These complexes were characterized using differtial scanning calorimetru, powder x-ray diffractometry and FTIR.
- **Cyprian O. Onyeji et al.** in 2009 stidoed amd omvestgate the possibility and extent of enhancement of the dissolution properties of Pyrimethaminne via complexation with the HPβ-CD as well as characterization of the complex formation of the drug with the cyclodextrin. The interaction between Pyrimethamine and HPβ-CD in solution

was studied by phase solubility analysis while binary systems of the compounds at 1:1 molar ratios were prepared by using the physical mixture, kneading, co evapouration. The binary systems were characterized using DSC, PXR and FTIR.

- **Dokes S. S.** in 2004 have prepared solid dispersion of macrolite antibiotic with β-CD, and cyclodextrin in different drug carrier molar ratio (1:1, 1:2, 1:3) by physical mixture method. The release rate for each antibiotic showed highest release in 1:3 ratio and the antibacterial activity of antibiotic ave also improved.
- **Camelia Nicolescu et al.** in 2010 to evaluate the possibility of enhanving the drug's solubility. Inclusion complexes between Rapaglinide and β-CD, HP, and RAMEB have been obtained by applying the following preparation methods: Liophylisation, co-precipitation followed by mend of NMR, DSC and FTIR.
- **Mukesh Chandra Sfhara et al.** 2011 studied solubility of candesafrtan using β-CD. The complexes were prepared by physical misture and freeze drying method. The physicochemical characterization of Candesartan-β-cyclodextrin inclusion complex was pperformed usig UV, FTIR, NMR and in vitro permeation experimettns through a synthetic membrane in both soid and solution phase.
- **J.S. Patil et al.** I 2010 studied influence of method of preparation o physicochemical proerrties and in vitro drug release profile of nimodipine cyclodextrin inclusion complexes using β-CD and HP-β-CD.

MATERIALS AND METHODS

Materials

Naproxen was supplied by SD, LAB Chemicals, Mumbai.

Phase solubility

Phase solubility studies were performed according to the method reported by Higuchi Connors. An excess amount of Naproxen was added to 10 ml distilled water containing various concentrations of β-CD (0-0.1 M) with or without fixed conc. of Leucine(0.2%w/v) in stopper tubes and mixture were shaken for 24Hrs $37\pm0.5℃$ at 150 rpm. After achieving equilibrium the solution was filtered through 0.45µm membrane filter paper. The sample was diluted suitably and assayed for content Naproxen by U.V. Spectrophotometer at 232 nm. The solubility constant and complexation efficiency was calculated by using the following equations.

$$Ks=\frac{Slope}{So(1-Slope)}$$

Ks=Stability constant

So=solubility of Naproxen in absence of CD

$$CE=\frac{Slope}{(1-Slope)}$$

CE=Complexation Efficiency

Kneading method

For preparation of ternary complex, Naproxen, $\beta-CD$ and Leucine in required quantity, were wetted with minimum quantity of water in order to obtain pasty mass. To evaluate the effect of trituration time, kneading was carried out for 30 and 60 min, respectively. Afterwards, obtained powders were kept for drying at $50℃$ for one day, further they were crushed, sieved(60#) and stored in desiccators at $25\pm2℃$.

Aqueous solubility

An excess amount of prepared binary and ternary complex added into 10ml water in stopper tubes. They were kept and shaking to achieve equilibrium appropriate aliquots was withdrawn filtered through Whatman filter paper no. 41. The filtrate analysed spectrophotometrically 232nm.

Dissolution Studies

Dissolution studies were performed according to the USFDA dissolution method for Naproxen. The dissolution rates of Naproxen and solid systems were measured in a dissolution apparatus (Lab India) using the paddles. Dissolutionstudies were carried out using 900 ml of 0.2M NAOH at $37\pm0.5℃$ at 50 rpm. At fixed time intervals (15, 30, 45, 60, 75 and 90 min) 5 ml sample were withdrawn. The dissolution medium was 5 ml aliquot with 5 ml fresh 0.M NAOH. The dissolution was immediately filtered $0.45\mu m$ membrane filter suitably diluted and were determined spectrophotomerically 232 NM.

Fourier transformation – infrared spectroscopy (FTIR)

FTIR studies were performed to determine the compatibility study between drug and other components by KBR dispersion method considering % transmittance of FTIR spectrophotometer (IRAffinity 1, Shimadzu, Japan). The base line correction was completed using dried potassium bromide and % transmittance analysed at in the spectral region of 4000-400 cm -1 using a resolution of 4cm-1 and 40 cm-1 scans.

RESULT AND DISCUSSION

Phase solubility studies[13]

Phase solubility diagram of binary mixture of Naproxen and β-CD and ternary complex with (0.2%) Leucine is done by Higuchi Connors method. Phase solubility diagram for binary and ternary inclusion complex is A1 type, which indicates that formation of soluble complex.

The shape of solubility curve may indicate that 1:1 molar ratio is most probable for the inclusion complex formed. According to Higuchi Connors equation the calculated solubility constants.

Table 1: Effect of polymer, Leucine on slope of phase solubility diagrams and stability constant (Ks) for binary and tertiary system of Naproxen with β-CD.

System	Slope	r^2	Ks(M1) Mean±SD	Kts/KBS	C.E
Naproxen β-CD					
Naproxen β-CD-LEUCINE					

KTS/KBS ratio of Ks for ternary and binary complexes; indicates mean of three readings; S.D.: Standard deviation. P value compared to Naproxen-β-CD i.e. significant C.E.: Complexation efficiency.

An indication of the process of transfer of Naproxen from pure water to aqueous solution of β-CD was obtained from the values of Gibbs free energy change.

Drug content

The percentage of drug content of kneading binary and tertiary system was found between.

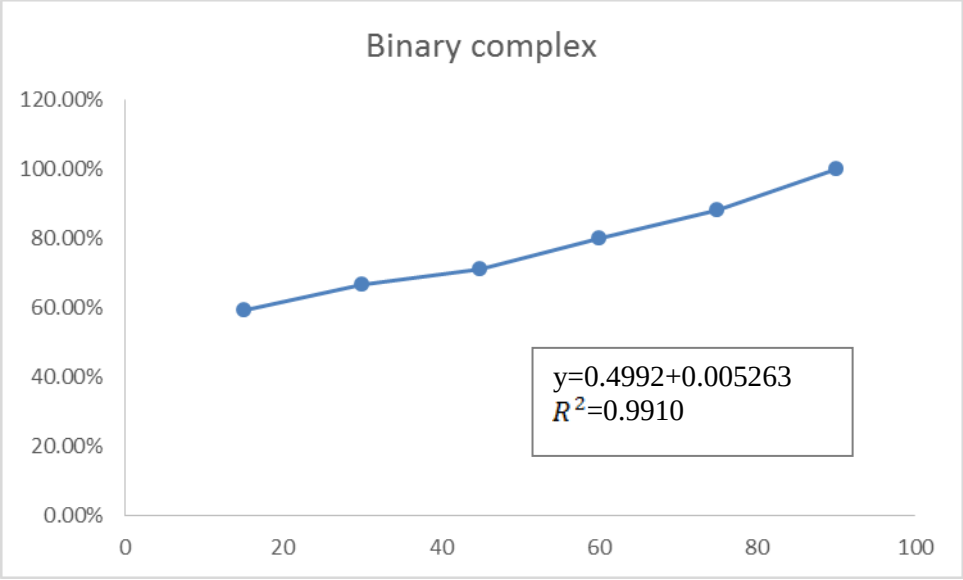
Aqueous solubility

The solubility studies of Naproxen with β-CD in binary and tertiary system with 0.2% w/v Leucine in water showed an enhancement in solubility as compared to pure drug alone. The 1:1 inclusion complex of Naproxen inclusion complex with or without Leucine showed higher solubility than their pure drug alone, the enhancement of solubility of complex mainly attributed due to the formation of stable inclusion complex of Naproxen and β-CD. The solubility constant suggests that β-CD and Naproxen have sufficient affinity towards each other to form a stable inclusion complex. In ternary system Leucine not only enhances their complex efficiency but also enhance their binding towards the β-CD.

System	Solubiliity in water at 25^{o}C mg/ml (mean ±SD)
Naproxen	In water
BK(binary)	In Water
BK(tertiary)	In Water

Dissolution studies

The comparative in vitro dissolution profiles of Naproxen. kneaded binary and tertiary complexes n 0.2M NAOH. It is clearly shown that the dissolution profile of the pure drug sample was 64% after 15min. It was interesting to note that in case of kneading binary complex. the dissolution complex was more than 90% er60min. And that of ternary complex showed the dissolution profile for kneaded complex more than 90% after 90 min. The kneaded complexes showed higher dissolution rate In the presence of β-CD the hydrophobic portion cyclodextrin cavity to form an inclusion complex, whereas at the same time, the hydrophilic portion lowers the aqueous surface tension by acting as a surfactant towards the cyclodextrin complexes and thus increasing its wettability and dissolved.



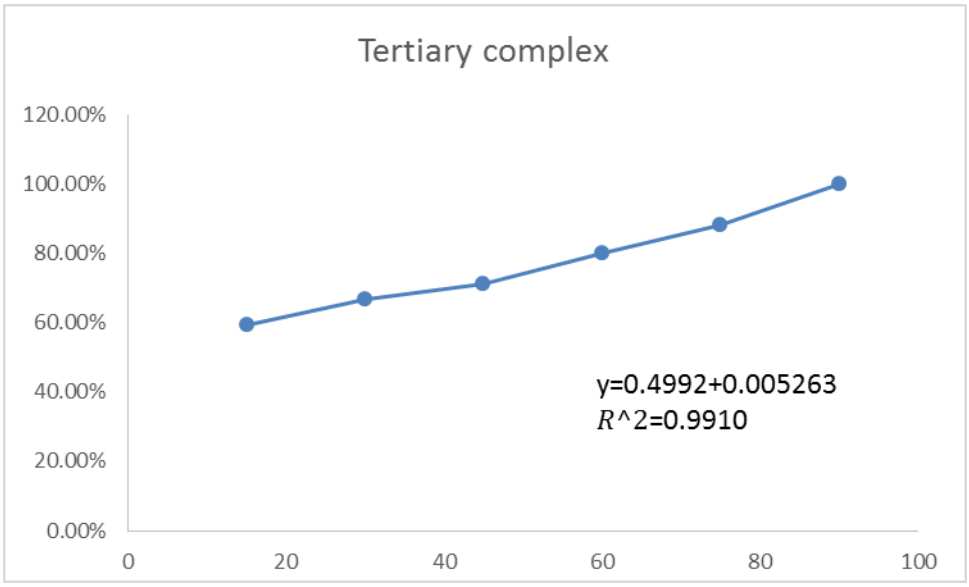


Fig: The dissolution diagram of Naproxen β-CD binary system and with Leucine ternary system at 37±0.5°C.