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Preparation and in Vitro Evaluation of Etodolac Nanoparticles

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Abstract

Etadolac nanoparticles were prepare by using solvent antisolvent precipitation method,in order to decrease particle size and increase dissolution rate which its rate limiting step in drug bioavailability. Different type of stabilizers used in this study, pvpk30, poloxamer188, HPMCE5, HPMCE15 and HPMCE50. Formulated nanosuspensions were characterize for particle size, poly disperse index(PDI) and specific surface area(SSA). The prepared nanoparticles were characterized by FTIR, SEM, DSC, invitro dissolution rate, and particle size measurement. The results show all particle size within nanosize from from39.5nm to 986nm, with entrapping efficiency range from 90.5% to 98.85%, and dissolution rate at 10min.was 85% for etodolac nanoparticles, and 15.8%, 35% for pure etodolac and physical mixing of drug and polymer, respectively. The results indicate a suitability of precipitation method for preparation of etodolac nanoparticles with enhancement of solubility and dissolution rate.

Keywords: *Invitro*, Etodolac Nanoparticles, Evaluation

Introduction

The major challenge in the formulation of oral dosage form is poor water solubility of drug lead to poor dissolution rate and poor in a bioavailability of drug and cause poor drug efficacy and consequent therapeutic failure [1], [2]. Development in the field of science of pharmaceutics led to establishment a number of techniques for solve problem of poor water solubility of drug [3]. The active pharmaceutical ingredients that have poor aqueous solubility are become more prevalent in the research and by pharmaceutical companies [4] and these challenge expected to be increase because of 40% of new chemical entity being generated by programmed of drug discovery are poor aqueous solubility [5].Solubility is a incident of dissolution of solute in solvent to produce a homogenous mixture, is one of a most important parameter to obtain a desire concentration of drug in systemic circulation to give a desire pharmacological response [6],[7]. However the drug to be absorbed should be in a form of solution at absorption site . There are a various techniques were used for improvement solubility of poor water soluble drug which include physical and chemical approaches like reduction in particle size, micronization[8], crystal engineering [9], salt formation [10],[11], solid dispersion [12],[13], use a surfactant [14], complexation[15], [16], [6].For drugs belong to BCS class II with low solubility and high permeability,

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dissolution rate is the rate limiting step for drug absorption. So when drug administration as oral dosage form, pharmaceutical preparation play a critical role in absorption from GIT(gastrointestinal tract) [17]. So one of the method to solve these problem of poor aqueous solubility by reduction in particles size cause increase in the specific surface area and hence increase in dissolution rate [18]. Nanoparticles have a particle size range from 10-1000nm in which the drug dissolve, entrapped, in capsulated according to the method of nanoparticles preparation [19]. Nanosuspension represent a promising strategy for delivery of hydrophobic drugs because of their versatile feature with unique advantage. Many techniques were used to preparation of nanosuspension like media milling and high pressure homogenizer [20],[21], Inflammatory arthritis can be express as a group of diseases that includes rheumatoid arthritis, ankylosing spondylitis and poriatic arthritis. When inflammation occurp in body, the immune system of body became to fight the infection attacks joints. However make swelling of joint, stiff and painful [22]. In general, in rheumatoid arthritis the first affect was small joint of hands and feet. In the other hand, for ankylosis spondylitis, the most affect joint is the joint of spine[23]. Etodolac is a pyranocarboxylic acid belong to NSAID which have effected in treatment of rheumatoid arthritis[24] and osteoarthritis,its selective COX2 inhibitor [25],[26]. Its a white crystalline powder, practically in soluble in water with pKa 4.65, belong to class II BCS[27]The aim of these study to preparation of etodolac nanoparticles for dissolution rate enhancement.

Keys word: Etodolac nanoparticles, solubility, dissolution rate.

material and method

material

Etodolac was purchase from Shenzhen lodi chemical CO.Ltd. India. Pvpk30, polyxamer188,HPMCE50.HPMCE15 and HPMCE5 were purchase from shanghai send pharmaceutical technology co.Ltd China. Potassium Dihydrogen Phosphate and Disodium hydrogen Phosphate were purchase from SPINE- CHEM. Limited and BDH laboratory supplies England respectively.Methanol supplied by GCC analytic reagent UK.

Saturated solubility of etodolac

Shake flask method was used to determine the saturated solubility[28],[29].Saturated solubility of etodolac was determined in water by using shake flask method. In conical flask, put 10ml of distilled water and added excess amount of etodolac powder and sealed well and allow to shaking for 48hr.at 37^0C[30]. Aliquot was filtered by using filtered paper o.45µm, then further dilution and then analyze by using UV spectrophotometer atwave length 278nm.

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Preparation of etodolac nanoparticles

Etodolac nanoparticles were prepared by use solvent antisolvent precipitation method. Organic phase was consist of etodolac in 5ml organic solvent (methanol), aqueous phase consist of polymer dissolve in water, follow that organic phase was add drop by drop on aqueous phase and then allow to agitate on magnetic stirrer at 500 rpm. Precipitation of etodolac in water with polymer was occurred due to etodolac water in soluble. Different type of polymers with different ratio(weight:weight) at (1:1,1:2 and 1:3) were use in the preparation of etodolac nanoparticles.

Measuring of particle size and polydispersity

Polydispersity index(IP) , particles size and specific surface area(SSA) were determined by using ABT-9000 NanoLaser particle size analyzer (Angstrom Advanced Inc USA). All measurement was done at scattering angle 90^0 with a constant temperature 25 ^{0}C without dilution.

Freeze dry of nanosuspension to obtain etodolac nanoparticles

The most appropriate method to obtain dried nanoparticles was freeze dryer. in which a sample of nanosuspension was putting in cell of lyophilizer and keep in deep freeze -80 ^{0}C for 24hr., follow that put in lyophilizer (LABCONCO) for 72hr. at condenser temperature -40 ^{0}C and pressure (0.9 mbar).

Determination of drug content in lyophilized powder

Precise amount of etodolac nanoparticles equivalent (10mg) dissolved in 10 ml of methanol follow that sonicated for 30 min. and diluted with appropriate volume of methanol and read in UV/visible spectrophotometric at 280nm to detect the amount of etodolac in lyophilized powder.

Scan electron microscope (SEM)

Morphology of particles can be determine by using SEM, INSPECT S50 was used in which sample put in double side tape carbon and its covered with gold.

Fourier transforms infrared spectroscopy (FTIR)

Chemical compatibility can be detected by using FTIR technique, sample mix with KBr and applied hydraulic pressureto get pellets and then scan at 400-4000cm^{-1}[31],[32] .

Deferential scanning calorimeter (DSC)

METTELER DSC30 was used, in which sample (5mg) putting in aluminum pan and allow the temperature to elevated from (30-200^{0}C) with heating rate (10^{0}C/min.)[33].

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In vitro drug release

Dissolution apparatus type 2 was used to study drug release. Accurate amount of sample of dried etodolac nanoparticles equivalent to(100 mg) was put in hard gelatin capsule in media contain 900 ml of 0.1N HCl (pH1.2) at 37^0C ±0.5 at 50rpm. Sample withdrawal (5ml) at specific interval time (2,5,10,20,25,30,45 and 60 min.) follow that filtered by filter paper 0.45 µm , then the sample analyzed at by UV spectrophotometer (1600Shimadzu, Japan). Fresh prepare medium was added after each withdrawal to maintains the volume of media constant. Pure etodolac powder and physical mixture (drug:polymer) were used for compare.

Result and discussion

Measuring particles size

For all formulas of etodolac nanoparticles were appeared within nano size range from (39.5nm-986nm) as show in tablet(1). The smallest formula size (39.5)for formula F6 with SSA(46.5)and PDI (0.008), while largest particle size for formula F15 986 nm with SAA(1.45) and PDI(0.009). The lowest PDI mean the highly uniform in particle size distribution. PDIfor all formulas was less than 0.2 mean monodisperse distribution with a good physical stability.

Effect type and concentration of polymer used

In order to optimize both type and concentration of polymer different type of stabilizer used (PVPk30, poloxamer188, HPMCE5,HPMCE15 and HPMCE50)with different ration of drug:polymer (1:1, 1:2, and 1:3). The results appeared that formula F6(etodolac:poloxamer188) at ratio (1:3) the smallest one has size 39.5nm with SSA(46.5) and PDI(0.008), so selected as a best formula. Polyxamer188 act as a mechanical barrier that providing a steric stabilization by methyl groups[34]. These results may be due to increment in polymer concentrationcause rapid absorption on the surface of molecules.Furthermore, this hinderin crystallization by prevent absorptionof drug molecules in crystal lattice which cause smaller particle size [35]. For PVP k30, increase concentration of polymer cause increase particle size for formulas (F1,F2 and F3) excess in polymer cause increase thickness of protective layer on the surface of molecules[36]. For HPMC(E5,15.50) increase concentration of polymer cause increase particle size andthis may be due to increment in polymer concentration cause increase in osmotic pressure which lead to enhance attraction between colloidal particles, however, increase in particle size occur[37],[38]

Table (1) etodolac nanoparticles, particle size, SSA, and PDI

Formula no.	Average Particle size (nm)	SSA m2/g	PDI
1	152	15.11	0.01
2	281	7.62	0.009
3	315	6.65	0.012

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4	282	7.88	0.01
5	99.5	24.73	0.019
6	39.5	46.5	0.008
7	425	5.57	0.025
8	507	4.38	0.061
9	578	3.352	0.015
10	532	4.17	0.008
11	632	3.43	0.023
12	675	4.19	0.011
13	795	2.71	0.005
14	806	2.52	0.043
15	986	1.45	0.009

Entrapment efficiency

Entrapment efficiency can be detected by ratio of mess of drug in nanoparticles to the mass of drug initially. The result obtain entrapment efficiency was ranged from 90.5% to 98.85%, for formulas of etodolacnaoparticles mean a suitability of polymer used and technique of solvent antisolvent precipitation method for preparation of etodolac nanoparticles.

Drug content in lyophilized powder

Drug content for selected formula F6 was (99.3%), refer to asuitability of antisolvent method to preparation of etodalac nanoparticles.

Saturated solubility

Saturated solubility was done for pure etodolac powder and lyophilized powder of formula F6(smallest particle size) in distilled water. the results obtain show increase in saturated solubility approximately 12 time as compare with pure etodolac powder. Saturated solubility of pure etodolac powder 0.0311mg/ml, in water. While for F6 0.373mg/ml in water. This increment in saturated solubility result from reduction of particles size cause increase surface area and increase saturated solubility according to Noyes Whitney equation[39].

FTIR

FTIR spectrum was done for pure etodolac and for lyophilize powder of F6 (best formula). For pure etodolac powder characteristic absorbance peak appear at 2975 cm^{-1}, 2930 cm^{-1} for (C-H) asymmetrical and symmetrical stretch vibration, respectively. For (C=O) carbonyl group at 1735 cm^{-1} . The O-H bending 1409 cm^{-1} , (C-O) stretch vibration 1034 cm^{-1}, and for (C-N) stretch band at 1260cm^{-1}. These result was similar for many studies [40],[3]. Most principle bands were appeared in FTIR of F6 for drug

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and polymer with little reduce in intensity of peaks, this mean no interaction occurred between drug and polymer. As show in figure(1).

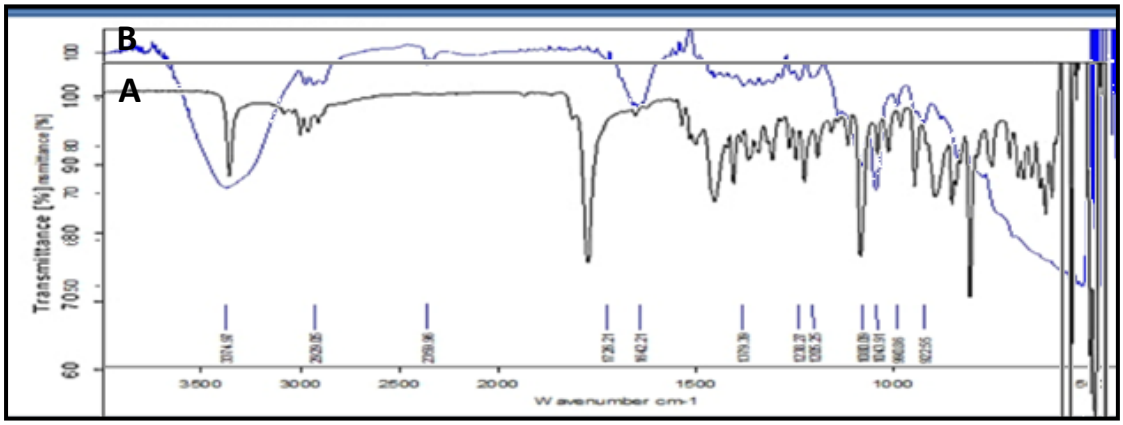
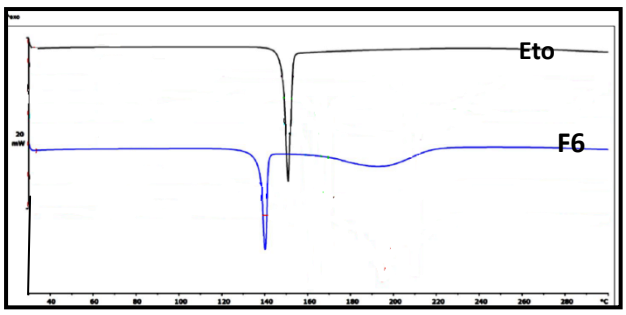


Figure (1) FTIR for A: pure etodolac powder, B: F6(etodolac nanoparticles)

DSC

DSC thermogram studies were done for pure etodolac powder and for lyophilized powder of selected formula (F6). As show in figure(2), the results obtain that single sharp endothermic peak at 154^0C, these result near to the result by study other study[3], while for lyophilized powder of F6, a decrement in enthalpy was noted when poloxamer188 used in F6 and these result also noted by study[30]. The possible explanation may be dissolution of drug with stabilizer at higher temperature [41]or may be converted of drug from crystal to amorphous state[42]



Figure(2) DSC of pure etodolac powder and for F6

PXRD

PXRD were conducted for pure etodolac powder and for selected formula F6 (etodolac:poloxamer) at ratio(1:3), the results as appeared in figure(3), show several sharp peaks at diffraction angle 2θ 9.4^0, 13.6^0, 14.5^0,16.7^0, 18.9^0,23.1^0 and 27.4^0these mean crystalline form of etodolac pure powder, these result also obtain by some studies[43]. While for formula F6 show a reduction in intensity of peak which mean converted drug from crystalline to amorphous state and improve dissolution of drug[44], these result agreement with result obtain by DSC.

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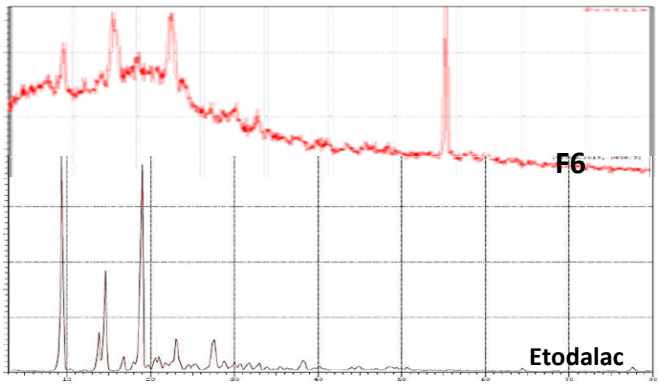
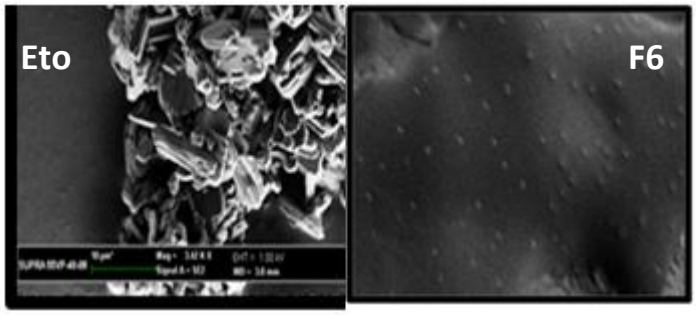


Figure(3) PXRD for pure etodolac powder and for F6 formula

SEM

SEM was used to determine morphology with topography of drug and nanoparticles. Figure (4) for pure etodolac show a regular crystal shape of particles and large particles size, while for formula F6 SEM show a spherical particle shape with no aggregation of particles occurred.



Figure(4) SEM for Etodolac pure powder and F6

In vitro release of drug

Invitro drug release was conducted for pure etodolac drug, physical mixture (PM) of drug and polymer (drug and poloxamer 188) and for optimum formula of etodolac nanoparticles(F6). The results obtain show at 10min. the drug release about 85% for formula F6 and , 15.8% and 35% for pure etodolac drug and PM of drug and polymer, respectively, as show in figure(5). However, these increase in dissolution rate of etodolac nanoparticles as compare with pure etodolac and PM of drug and polymer result from reduction in particle size cause increase in surface area and increase dissolution of drug release.

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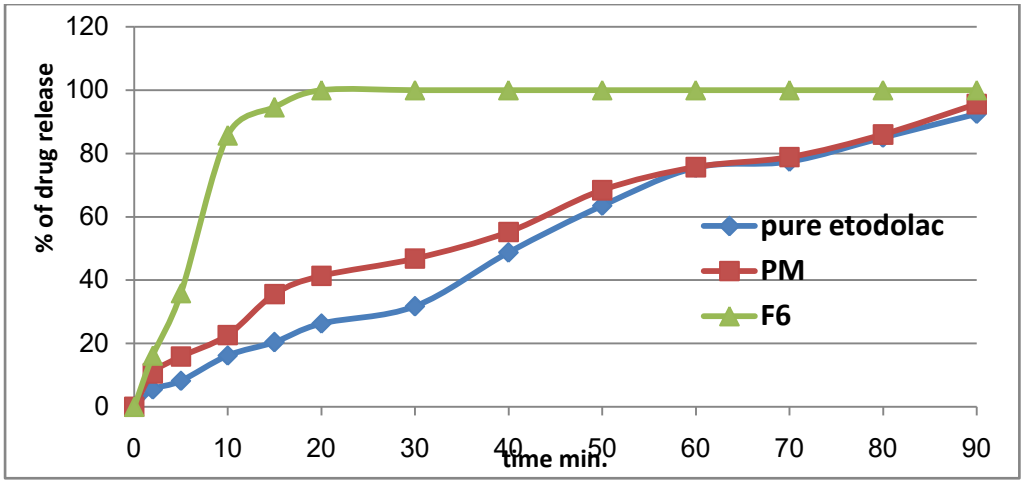

Figure(5) Invitrodrug release of etodolac pure powder, PM and F6 at 0.1NHCl

Conclusion

The results from this research demonstrate a successful preparation of etodolac nanoparticle with size ()nm with poloxamer 188 by solvent antisolvent method. The FTIR result show a chemical compatibility between drug and polymer, and no chemical interaction occurred. DSC appeared a good compatibility between drug and polymer and converted of drug from crystal to amorphous state, also these result confirm by PXRD. SEM show a reduction in particles size with spherical shape of particles with no sign of aggregation. Reduction in particle size cause increase in surface area and improve dissolution rate and so increase bioavailability of drug.

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