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Case Report

IN-VITRO DISSOLUTION ENHANCEMENT OF NIMESULIDE USING HP-β-CD BY KNEADING METHOD

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A R T I C L E I N F O

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A B S T R A C T

The purpose of the current investigation was to enhance in vitro dissolution rate of nimesulide using HP-β-CD. Nimesulide is widely used as antiarthritics, antipyretic and spondylitis. Nimesulide is BCS class II drug having low solubility, low bioavaibility and low dissolution rate. For improving solubility and enhancement of dissolution rate of drug derivative of cyclodextrin was used to prepare complex. Here, kneading method was used for formulation. Different batch of different concentration of HP-β-CD was prepared and we get batch B_3 having enhanced dissolution rate of Nimesulide compare to all other batches.

INTRODUCTION

Nimesulide is chemically 4'-nitro-2'-phenoxy methane sulfonanilide a weakly acidic non-steroidal anti-inflammatory drug. It contains a sulfonanilide moiety as the acidic group rather than a carboxylic group which differs it from other non-steroidal anti-inflammatory drugs (NSAIDs).[1] Nimesulide have poor solubility in water (≈ 0.01 mg/mL).[2,3] The poor aqueous solubility and wettability of nimesulide is a major problem associate to formulate pharmaceutical formulations for oral or parenteral delivery which shows variable bioavailability.[4] To overcome these drawbacks increasing the aqueous solubility of Nimesulide is an important goal. Nimesulide is majorly used as a anti-inflammatory[5], antipyretic and analgesic drug having moderate incidence of gastric side effect.[6,7]

Cyclodextrins are the oligosaccharide widely used to improve solubility of insoluble drug by forming inclusion complex.[8] Cyclodextrins molecules have hydrophobic inside and hydrophilic outside which foams cavity like structure which helps to entrap guest molecule in the internal cavity.[9] Cyclodextrin is improves solubility of drug which cause increase in bioavaibility of active molecule which leads to enhance dissolution of drug.[10,11] Different grade of cyclodextrin have different no of sugar ring molecules.

Dissolution enhancement is a crucial function for enhance bioavaibility of poorly soluble drugs.

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Dissolution enhancement method will increase effective surface area of the drug, which can achieved different methods like solute-solvent complexation method, polymorphism, molecular encapsulation with cyclodextrin, complexation with Cyclodextrins, inclusion complexation method using cyclodextrin compound are conventional and easy method compare to all other methods [12] different- different approaches are used for formulation of inclusion complex such as Physical blending method, Kneading method,[13] Co-precipitation technique,[14] Solution/solvent evaporation method, Neutralization precipitation method, Milling/Co-grinding technique,[15] Atomization/Spray drying method,[16] Lyophilization/ Freeze drying technique, Microwave irradiation method, Supercritical antisolvent technique.

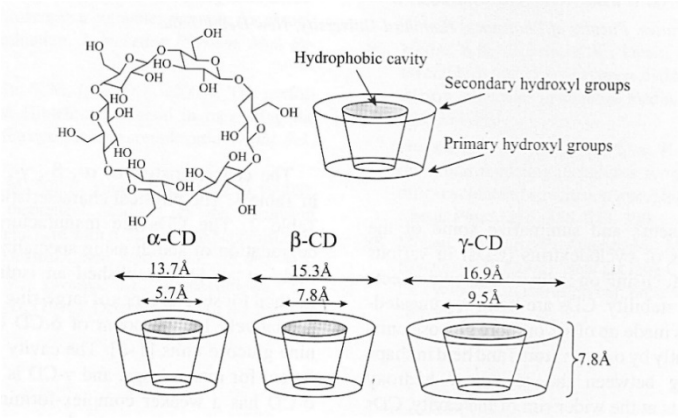

Figure 1 Structure of Cyclodextrin[17]

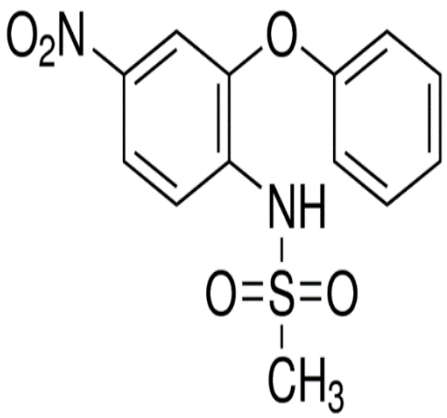

Figure 2 Structure of Nimesulide[18]

MATERIALS AND METHODS

Materials: Nimesulide was obtained as a gift sample from Zydus hetero drugs ltd Hyderabad. Cyclodextrins was obtained as a gift sample from Sunrise Remedies Pvt. Ltd. Cross Carmalose, Lactose, Talc, Mg. Stearate were of analytical grade.

Methods

Preparation of Solid Binary Systems[19]*:* The following binary systems of Nimesulide and HP-β-CDs were prepared at 1:1 and 1:2 molar ratios (1:1 and 1:2 M).

Physical Mixtures[20]*:* The physical mixtures of Nimesulide and HP-β -CDs in 1:1 and 1:2 M were obtained by mixing individual components that had previously been sieved (75-150 μm) together with a spatula.

Kneading System[14,19]***:*** Nimesulide and HP-β -CDs were triturated in a mortar with a small volume of a solvent blend of water-methanol (3:2). The thick slurry was kneaded for 45 min and then dried at 55 ^{o}C until dry. The dried masswas pulverized and sieved through mesh no.120.

Preparation of Nimesulide tablet[2,19]***:*** Accurately weigh 50 mg of Nimesulide and required quantity of HP-β-CDs to foam inclusion complex by kneading method. Add required quantity of excipient given in Table 1. In batch B_1 Nimesulide is alone used to check dissolution profile of drug with suitable excipient. In batch B_2 Nimesulide- HP-β-CD is used in (1:1) ratio and in and B_3 Nimesulide- HP-β-CD is used in (1:2) other excipient are used in required quantity as per GRAS. Lactose was used as filler, Cross carmalose (5%), talc (2%) and magnesium stearate (2%) were incorporated, respectively as disintegrant and lubricants. Purified water was used as granulating fluid in wet granulation method. The tablet granules were compressed into tablets.

Table 1 Formula of Nimesulide Tablets Prepared by Wet Granulation Employing Drug- HP- β- CDs Inclusion Complexes

Ingredient (mg / tablet)	Nimesulide Tablet Formulation		
	B_1	B_2	B_3
Nimesulide	50	50	50
HP-β–CDs	-	50	100
Crosscarmalose	5%	5%	5%
Lactose	200	200	200
Talc	2%	2%	2%
Magnesium stearate	2%	2%	2%

Evaluation of Dosage Form

Hardness:[20] Hardness of the prepared tablets was determined using Pfizer hardness tester. Five tabletswere tested for hardness from each batch and the mean value was calculated.

Thickness:[21] Thickness of tablet was measured using vernier calipers. Three tablets were selected at random from each batch and the mean value was calculated.

Friability:[22] Pre weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dedusted, reweighed and % friability was calculated.

Weight variation:[23] Twenty tablets were selected randomly and weighed individually to check for weightvariation and then the average weight was determined. Percentage deviation of individual tablet from average weight was calculated. Tablets meet USP specifications if not morethan 2 tablets are outside the percentage limit and if no tablets differ by more than twice the percentage limit.

Disintegrating Test:[23] To determine disintegration time tablet was placed in a Petridis containing 10 ml of Phosphate buffer (7.4) at 37ºC ± 2ºC, the time in second taken for complete disintegration of the tablet was measured in seconds.

Phase Solubility Studies:[15,24] Excess amounts of Nimesulide (50 mg) were added to 15 ml of purified water or CD aqueous solutions (0.003-0.048 M concentration range) taken in a series of 25 ml stoppered conical flasks and the mixtures were shaken for 48 hours at room temperature (28°C) on a rotary flask shaker. After 48 hours of shaking to achieve equilibrium 2 ml aliquots were withdrawn at 12- hour intervals and filtered immediately using a 0.45- μm nylon disc filter. The filtered samples were diluted suitably and assayed for N by measuring absorbance at 397 nm. Shaking was continued until 3 consecutive estimations were the same (96 hours). The solubility experiments were conducted in triplicate (coefficient of variation, CV < 2%). The blanks were performed on the same concentrations of CDs in water so as to cancel any absorbance that may be exhibited by the CD molecules. The apparent stability constants were calculated from the phase solubility diagrams.

Calibration curve of Nimesulide[27]*:* The calibration curve of Nimesulide was prepared in phosphate butter pH 7.4. For this 250 ml of 0.2 N potassium dihydrogen phosphate and 195.5 ml of 0.2 N sodium hydroxide was taken and placed in 1000 ml volumetric flask and then distilled water was added to make up the volume. For determination of absorption maxima, a solution of 10 microgram/ml of Nimesulide in PBS was prepared and then absorbance is determined from 200 nm to 400 nm Using U.V spectrophotometer. Then 100 mg of Nimesulide was weighted accurately and dissolved in 10 ml of methanol (10% v/v) and 90 ml of phosphate buffer pH 7.4 (PBS). Volume was make up 100 ml by PBS. Then 1 ml of this solution was diluted to 10 ml by 10% methanolic buffer pH 7.4 to produce 100 μg/ml stock solution. From this stock solution, aliquots of 2.5 ml, 5 ml, 7.5 ml, 10 ml, 12.5 ml, 15 ml, 20 ml, 25 ml and 30 ml were taken and diluted suitably by 10% v/v methanolic solution of phosphate buffer pH 7.4. The calibration curve was plotted b/w concentration and absorbance.

Dissolution Study[27]*:* Dissolution rate of Nimesulide -HP-β-CD tablets was studied using an USP XXIII 6 station dissolution rate test apparatus (Electro Lab) with a paddle stirrer. The dissolution rate was studied in 900 ml of phosphate buffer pH 7.4at a speed of 50 rpm and a temperature of 37 ^{0}C ± 10 ^{0}C. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45m) at different time intervals, suitably diluted and assayed for Nimesulide at 397 nm. The dissolution medium withdrawn at each sampling time is replaced with fresh drug-free dissolution fluid. The dissolution experiments were conducted in triplicate.

RESULT

Table 2 Tablet Evaluations

EVALUTION TEST	B_1	B_2	B_3
Weight variation	Pass	Pass	Pass
Hardness of tablet	4	3	4
Friability	0.71	0.78	0.82
Thickness of the tablets	1.7mm	1.3mm	1.4mm
Disintegration Time	57sec	49sec	45sec

Table 3 Phase solubility

Conc.	abs.-at 18hr	abs.-at 48hr	conc. at 18 hr	conc. at 48 hr
0	0.081	0.097	0.0621	0.0781
0.005	0.117	0.109	0.0981	0.0901
0.01	0.131	0.14	0.1121	0.1211
0.02	0.142	0.17	0.1231	0.1511
0.03	0.159	0.24	0.1401	0.2211
0.04	0.178	0.287	0.1591	0.2681
0.05	0.211	0.392	0.1921	0.3731

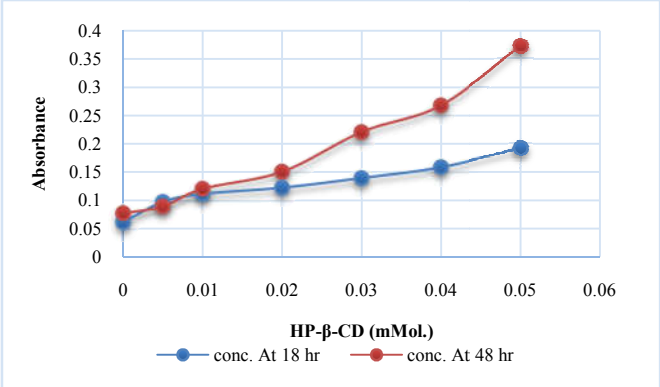

Figure 3 Phase Solubility study of Nimesulide using Different molar concentration of HP-β-CD

Table 4 Calibration curve

Concentration (µg/ml)	Absorbance
0	**0**
2	0.125
4	0.227
6	0.312
8	0.42
10	0.545
12	0.612
14	0.698
16	0.869
18	0.995

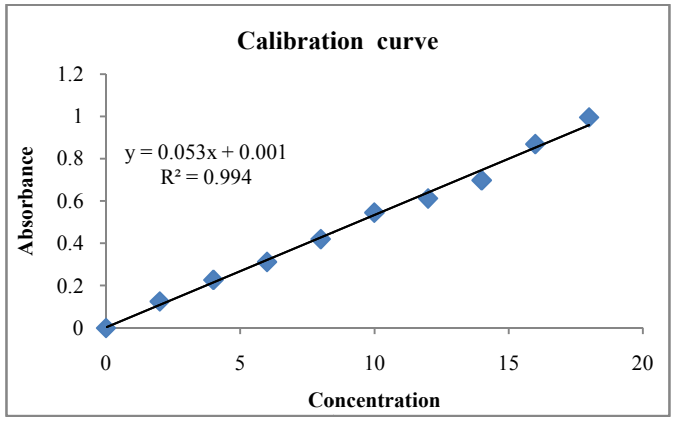

Figure 4 Calibration curve of Nimesulide

Table 5 % Cumulative drug release

TIME (min)	%CPR		
	B_3	B_2	B_1
0	0.00	0.00	0.00
5	5.875472	3.464151	3.769811
15	25.67547	13.31321	14.43396
30	45.61132	24.82642	27.13585
45	64.22264	39.63396	40.07547
60	81.57736	53.83019	52.57358
75	97.53962	67.17736	64.56226
90	109.6981	80.28679	75.43019

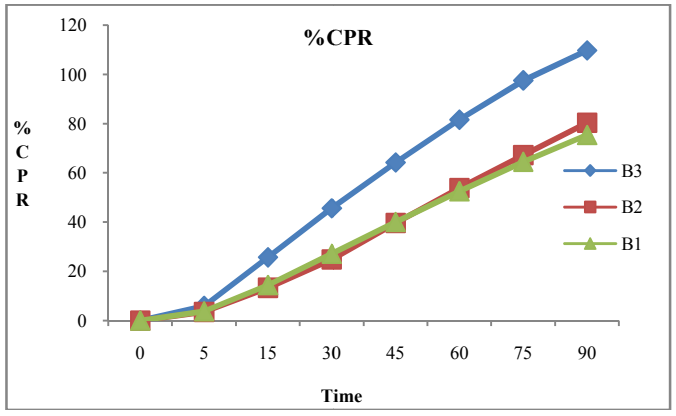

Figure 5 Cumulative % release of Nimesulide different batches of Nimesulide inclusion complex

CONCLUSION

Nimesulide is BCS Class II drug having a problem of low solubility and low dissolution rate. The aim of the work was to improve the dissolution rate of Nimesulide which was required for improving the dosage form characteristics. Here, kneading technique was used for this work due to its ease of preparation and ease of optimization. As Nimesulide alone cannot produce satisfactory dissolution rate, we prepare inclusion complex of nimesulide with HP-β-CD using different polymer ratio which shows enhancement in dissolution rate of nimesulide as well as in % drug release. Among all 3 batches as B_1, B_2, B_3 the optimized batch was B_3 though it show enhanced dissolution. Also from the graph of phase solubility study of nimesulide using different molar concentration of HP-β-CD linear graph is obtained which shows improving in solubility and dissolution rate of nimesulide.

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