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A FACTORIAL STUDY ON ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF LORNOXICAM EMPLOYING HP-β-CYCLODEXTRIN AND SURFACTANTS

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ABSTRACT

Lornoxicam, a widely prescribed anti-inflammatory and analgesic drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. The objective of the present study is to enhance the solubility and dissolution rate of lornoxicam employing Hydroxy propyl β-cyclodextrin (HPβCD) and two surfactants (SLS and Tween 80) alone and in combination. The individual main effects and combined (interaction) effects of HPβ-cyclodextrin and surfactants on the solubility and dissolution rate of lornoxicam were evaluated in a series of 2^2 factorial experiments. The solubility of lornoxicam in the four selected fluids as per 2^2 factorial study in each case was determined (n=4). Lornoxicam-βCD-surfactant inclusion complexes were prepared employing the selected combinations of HPβCD and surfactant in each case as per a 2^2 factorial design and the inclusion complexes prepared were evaluated for dissolution rate and dissolution efficiency. Combination of Hydroxy propyl βCD with surfactants, SLS and Tween 80 has resulted in a much higher enhancement in the solubility of lornoxicam than is possible with them individually. ANOVA indicated that the individual main effects of HPβCD, SLS and Tween 80 as well as the combined effects in enhancing the solubility and dissolution rate of lornoxicam are highly significant ($P<0.01$). HPβCD alone gave 1.53 fold increase in the solubility of lornoxicam. Whereas in combination with SLS and Tween 80 it gave respectively 31.43 and 13.20 fold increase in the solubility of lornoxicam. Lornoxicam- HPβCD and lornoxicam- HPβCD- Surfactant complexes gave rapid and higher dissolution of lornoxicam when compared to lornoxicam pure drug. HPβCD alone gave an increase of 4.35 fold in the dissolution rate (K_1) of lornoxicam. Combination of HPβCD with SLS and Tween 80 has further enhanced the dissolution rate (K_1) of lornoxicam by 9.50 and 6.10 folds respectively. Hence, a combination of HPβCD with surfactants (SLS and Tween 80) is recommended for enhancing the solubility and dissolution rate of lornoxicam, a poorly soluble BCS Class II drug.

INTRODUCTION: About 95 % of all new potential therapeutics (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pHs and consequent low dissolution rate. These drugs are classified as class II drugs under BCS and pose challenging problems in their pharmaceutical product development process.

The drug in solid dosage form (tablet) must undergo dissolution before it is available for absorption from gastrointestinal tract. Dissolution forms the rate limiting step in the absorption of drugs from solid dosage forms especially when the drug is poorly soluble.

Several modern organic drugs belong to class II category under BCS and exhibit low and variable dissolution rates. These drugs need enhancement in dissolution rate and bioavailability to derive their maximum therapeutic efficacy.

Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nano-particles, nanosuspensions, micro emulsion and self-emulsifying systems are available to enhance the bioavailability of BCS Class II drugs.

Lornoxicam, a widely prescribed anti-inflammatory and analgesic drug belong to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically in soluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability.

Among the various approaches complexation with Hyroxy propyl β-cyclodextrin has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs.

Hydroxy propyl β-Cyclodextrins (HPβCD) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs.

As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected [1, 2].

HPβ-Cyclodextrin have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies [3, 4].

Surfactants also increase the solubility of lipophilic water-insoluble drugs by micellar solubilization. Though cyclodextrin complexation and use of surfactants for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate.

The objective of the present study is to enhance the solubility and dissolution rate of lornoxicam employing cyclodextrin (HPβCD) and two surfactants (SLS and Tween 80) alone and in combination. The individual main effects and combined (interaction) effects of HPβ-cyclodextrin and surfactants on the solubility and dissolution rate of lornoxicam were evaluated in a series of 2^2 factorial experiments.

Experimental:

Materials: Lornoxicam was a gift sample from M/s Amoli Organics Pvt., Ltd., Mumbai, HPβ-cyclodextrin was a gift sample from Signet Chemical Corporation Pvt., Ltd., Mumbai. Tween 80 (BDH) Sodium lauryl sulphate (SD Fine Chem.). All other materials used were of pharmacopoeial grade.

Methods:

Determination of solubility: The solubility of Lornoxicam in the following four selected fluids as per 2^2 factorial study was determined to evaluate the individual and combined effects of the HPβ-cyclodextrin and surfactants on the solubility of lornoxicam. The two levels of HPβCD (factor A) are 0 and 5 mM and the two levels of surfactant (factor B) are 0 and 2% w/v.

The selected fluids as per 2^2 factorial study are as follows:

For Lornoxicam-HPβCD-SLS system:

Statistical code as per 2^2 – Factorial Design	Description
(1)	Purified water
(a)	Water containing HPβCD (5mM)
(b)	Water containing SLS (2 %)
(ab)	Water containing HPβCD (5mM) and SLS (2%)

For Lornoxicam-HPβCD-Tween 80 system:

Statistical code as per 2^2 – Factorial Design	Description
(1)	Purified water
(a)	Water containing HPβCD (5mM)
(b)	Water containing Tween 80 (2 %)
(ab)	Water containing HPβCD (5mM) and Tween 80 (2%)

Procedure: Excess drug was added to 15 ml of the selected fluid taken in a 25ml stoppered conical flask and the mixtures were shaken for 72 hours at room temperature (28^0C) on a rotary flask shaker. After 72 hrs of shaking to achieve equilibrium, 2 ml of aliquots were withdrawn and filtered immediately using 0.45µ disc filter. The filtered samples were diluted suitably and assayed at 376 nm for lornoxicam. In each case the solubility determinations were replicate 4 times (n=4).

Preparation of Drug-HPβCD- Surfactant systems: To evaluate the individual and combined effects of HPβCD and surfactants on the dissolution rate of lornoxicam, drug-HPβCD-surfactant systems were prepared employing the following selected combinations of HPβCD and surfactant in each case as per a 2^2 factorial design. The two levels of HPβCD (factor A) are 0 and 1:2 ratio of drug: HPβCD respectively. The two levels of surfactant (factor B) are 0 and 2%. The following are the selected treatments as per 2^2 factorial design in each case to evaluate the individual and combined effects. The selected treatments (products) as per 2^2 – factorial study in each case are as follows.

For Lornoxicam-HPβCD-SLS system

Statistical code as per 2^2 – Factorial Design	Description
(1)	Lornoxicam pure drug
(a)	Lornoxicam-HPβCD (1:2) binary system
(b)	Lornoxicam-SLS (2%) binary system
(ab)	Lornoxicam-HPβCD-SLS (1:2:0.02) ternary system

For Lornoxicam-HPβCD-Tween 80 system:

Statistical code as per 2^2 – Factorial Design	Description
(1)	Lornoxicam pure drug
(a)	Lornoxicam-HPβCD (1:2) binary system
(b)	Lornoxicam-Tween 80 (2%) binary system
(ab)	Lornoxicam-HPβCD-Tween 80 (1:2:0.02) ternary system

The above mentioned binary and ternary systems were prepared by kneading method employing HPβCD, Tween 80 and SLS.

Preparation method: Required quantities of drug, HPβCD and surfactant were taken in a clean and dry mortar. Kneading fluid consisting of water: alcohol (1:1) was added and mixed to get thick slurry. The slurry was thoroughly mixed and kneaded for 45 min. Additional quantities of kneading fluid was added to maintain the mixture as thick slurry during the kneading process. After kneading for 45 min the mixture was transferred to a petridish and dried in an oven at 60^oC. The dried powder was passed through mesh No.100.

Estimation of Drug Content in drug-HPβCD-surfactant Complexes prepared: Drug HPβCD-surfactant complex powder equivalent to 50 mg of the medicament was taken into a boiling test tube and extracted with 4 x 10 ml quantities of methanol. The methanolic extracts were collected into 50 ml volumetric flask and the volume was made up to 50 ml with methanol. The solution was subsequently diluted with phosphate buffer of pH 6.8 and assayed for lornoxicam content at 376 nm. From each product four samples were analysed for drug content.

Dissolution Rate study on Drug-HPβCD-Surfactant Systems: The dissolution rate of lornoxicam from the drug-HPβCD-surfactant systems prepared was studied in phosphate buffer of pH 6.8 (900 ml) using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37°C ± 1°C was maintained throughout the study. Complex system equivalent to 50 mg of drug was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed for lornoxicam at 376 nm.

The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid. The dissolution experiments were replicated four times each (n=4).

RESULTS AND DISCUSSION: The objective of the present study is to enhance the solubility and dissolution rate of lornoxicam employing Hydroxy propyl β-cyclodextrin (HPβCD) and two surfactants (SLS and Tween 80) alone and in combination. The individual main effects and combined (interaction) effects of HPβ-cyclodextrin and surfactants on the solubility and dissolution rate of lornoxicam were evaluated in a series of 2^2 factorial experiments.

Solubility Studies: The results of solubility studies with HPβCD, SLS and Tween 80 are given in **Table 1**.

TABLE 1: SOLUBILITY OF LORNOXICAM IN VARIOUS FLUIDS (n=4) Containing HPβCD, SLS AND TWEEN80 AS PER 2^2 FACTORIAL STUDY

Fluid	Solubility (mg/100 ml) $\bar{x}$ ± sd	Increase in solubility (no. of folds)
Purified water	1.20 ± 0.09	--
Water containing HPβCD(5mM)	1.84 ± 0.31	1.53
Water containing SLS (2%)	36.45 ± 1.316	30.37
Water containing Tween 80 (2 %)	8.76 ± 0.195	7.3
Water containing HPβCD (5mM) and SLS (2%)	37. 72 ± 0.06	31.43
Water containing HPβCD (5mM) and Tween80 (2%)	15.85 ± .30	13.20

The solubility of lornoxicam was markedly enhanced by HPβCD and SLS. A 1.53 and 30.37 fold increase in the solubility of lornoxicam was observed respectively with HPβCD (5mM) and SLS (2%) when used alone. A combination of HPβCD (5mM) and SLS (2%) gave a 31.43 fold increase in the solubility of lornoxicam. The solubility data were subjected to Analysis of Variance (ANOVA) to find out the significance of individual main and combined (interaction) effects of HPβCD and SLS on the solubility of lornoxicam. ANOVA indicated that the individual main effects of HPβCD and SLS as well as the combined effects are highly significant (P<0.01).

The solubility of lornoxicam was also markedly enhanced by HPβCD and Tween80. A 1.53 and 7.3 fold increase in the solubility of lornoxicam was observed respectively with HPβCD (5mM) and Tween80 (2%). A combination of HPβCD (5mM) and Tween80 (2%) gave a 13.20 fold increase in the solubility of lornoxicam. ANOVA indicated that the individual main effects of HPβCD and Tween 80 as well as the combined effects were highly significant (P < 0.01). Combination of HPβCD with surfactants, SLS and Tween 80 has resulted in a much higher enhancement in the solubility of lornoxicam than is possible with them individually. This may be due to better inclusion of drug in CD molecules in the presence of surfactants. Thus combination of SLS with HPβCD resulted in a much higher enhancement in the solubility of lornoxicam than is possible with HPβCD alone. Hence, a combination of HPβCD and SLS is recommended for enhancing the solubility of lornoxicam, a poorly soluble BCS Class II drug.

Effects of HPβCD and Surfactants on the Dissolution Rate of Lornoxicam: To evaluate the individual main and combined effects of HPβCD and surfactants (SLS and Tween80) on the dissolution rate of lornoxicam, solid inclusion complexes of Drug-HP βCD -Surfactant were prepared in each case as per 2^2 factorial design. All the solid inclusion complexes prepared were found to be fine and free flowing powders. Low C.V values (< 1.5%) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared.

The dissolution rate of lornoxicam from various Drug-HPβCD-Surfactant complexes prepared was studied in phosphate buffer pH 6.8. Drug-HPβCD and Drug-HPβCD-Surfactant complexes gave rapid and higher dissolution of lornoxicam when compared to lornoxicam pure drug. The dissolution data were analyzed as per zero order and first order kinetics. Dissolution of lornoxicam from all HPβCD-Surfactant complexes prepared followed first order kinetics with correlation coefficient (r) values in the range 0.9223-0.9730.

The first order dissolution rates (K_1) and Dissolution efficiency (DE_{15}) values, calculated as per Khan[5], are given in **Table 2**. The dissolution rates (K_1) and Dissolution efficiency (DE_{15}) values were several times higher in the case of HPβCD-Surfactant complexes when compared to lornoxicam pure drug. The number of times that the DE_{15} and K_1 values were enhanced or increased by the HPβCD and surfactants individually and in combination are shown in Table 2.

Hence, a combination of βCD with surfactants (SLS and Tween 80) is recommended for enhancing the solubility and dissolution rate of lornoxicam, a poorly soluble BCS Class II drug.

Table 2: Increase in DE_{15} and K_1 values of Lornoxicam by HPβCD and Surfactants alone and in combination

CD complex	DE_{15} (%)		$K_1 \times 10^2$ (min^{-1})	
	$\bar{x}$	Increase (no. of folds)	$\bar{x}$	Increase (no. of folds)
Lornoxicam	1.83	-	0.20	
HPβCD	9.2	5.02	0.87	4.35
SLS	6.74	3.68	0.69	3.45
Tween 80	4.7	2.56	0.60	3.00
HPβCD-SLS	17.39	9.50	1.90	9.50
HPβCD-Tween 80	11.23	6.13	1.22	6.10

Among the individual effects, HPβCD gave higher enhancement in the K_1 and DE_{15} of lornoxicam than the surfactants (SLS and Tween80). The order of increasing enhancement in K_1 and DE_{15} observed was HPβCD > SLS > Tween 80.

The dissolution rate (K_1) values of various Drug-HPβCD-Surfactant complex systems were subjected to Analysis of Variance (ANOVA) to evaluate the significance of the individual main and combined effects of HPβCD and surfactants in enhancing the dissolution rate (K_1).

The results of ANOVA indicated that all individual and combined effects were highly significant ($P < 0.01$) except the combined effect of HPβCD-Tween 80 ($P > 0.05$). HPβCD alone gave an increase of 4.35 fold in the dissolution rate (K_1) of lornoxicam. Combination of HPβCD with SLS and Tween 80 has further enhanced the dissolution rate, (K_1) of lornoxicam by 9.50 and 6.10 folds respectively. Hence, a combination of HPβCD with surfactants (SLS and Tween 80) is recommended for enhancing the solubility and dissolution rate of lornoxicam, a poorly soluble BCS Class II drug

CONCLUSIONS:

1. Combination of HPβCD with surfactants, SLS and Tween 80 has resulted in a much higher enhancement in the solubility of lornoxicam than is possible with them individually.

2. ANOVA indicated that the individual main effects of HPβCD, SLS and Tween 80 as well as the combined effects in enhancing the solubility and dissolution rate of lornoxicam are highly significant ($P<0.01$) except the combined effect of HPβCD-Tween 80 in enhancing the dissolution rate.

3. HPβCD alone gave 1.53 fold increase in the solubility of lornoxicam. Whereas in combination with SLS and Tween 80 it gave respectively 31.43 and 13.20 fold increase in the solubility of lornoxicam.

4. Lornoxicam-HPβCD and lornoxicam-HPβCD-Surfactant complexes gave rapid and higher dissolution of lornoxicam when compared to lornoxicam pure drug.

5. HPβCD alone gave an increase of 4.35 fold in the dissolution rate (K_1) of lornoxicam. Combination of HPβCD with SLS and Tween 80 has further enhanced the dissolution rate (K_1) of lornoxicam by 9.50 and 6.10 folds respectively.

6. Hence, a combination of HPβCD with surfactants (SLS and Tween 80) is recommended for enhancing the solubility and dissolution rate of lornoxicam, a poorly soluble BCS Class II drug.

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