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ResearchArticle

FORMULATION DEVELOPMENT OF ETORICOXIB TABLETS EMPLOYING HP β CYCLODEXTRIN-POLOXAMER 407- PVP K30: A FACTORIAL STUDY

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ABSTRACT

Etoricoxib, a widely prescribed anti-inflammatory drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. The objective of the study is to evaluate the feasibility of formulating etoricoxib –HPβCD– Poloxamer 407 /PVP K30 inclusion complexes into tablets and to evaluate the effects of HPβCD, Poloxamer 407 and PVP K30 on the dissolution rate and dissolution efficiency of etoricoxib tablets in 2^3 factorial study. A comparative evaluation of wet granulation and direct compression methods was made for the preparation of tablets employing drug – HPβCD – Poloxamer 407 / PVP K30 inclusion complexes. Drug – HPβCD- Poloxamer 407 / PVP K30 inclusion complexes were prepared by kneading method. Tablets each containing 60 mg of etoricoxib were prepared by wet granulation and direct compression methods employing various HPβCD complexes as per 2^3 factorial design and the tablets were evaluated for dissolution rate and other physical properties.

Etoricoxib tablets formulated employing dug – HPβCD – Poloxamer 407 / PVP K30 inclusion complexes and prepared by direct compression method disintegrated rapidly when compared to those made by wet granulation method. Etoricoxib dissolution was rapid and higher from the tablets formulated employing drug- HPβCD- Poloxamer 407/ PVP K30 inclusion complexes when compared to the tablets containing etoricoxib alone in both wet granulation and direct compression methods. The individual as well as combined effects of the three factors involved i.e., HPβCD (factor A), Poloxamer 407 (factor B) and PVP K30 (factor C) were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of etoricoxib in both wet granulation and direct compression methods. Among the three factors Poloxamer 407 (factor B) gave highest enhancement in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of etoricoxib tablets in both wet granulation and direct compression methods. HPβCD alone gave low dissolution rates in both wet granulation and direct compression methods. Combination of HPβCD with Poloxamer 407 gave a significantly higher dissolution rate (K_1) of etoricoxib in both wet granulation and direct compression methods. Combination of HPβCD with PVP K30 also gave a significantly higher dissolution rate (K_1) of pioglitazone in the direct compression method. Overall direct compression method gave higher dissolution rates (K_1) and dissolution efficiency (DE_{30}) values than the wet granulation method in all the cases. Hence Poloxamer 407 alone or a combination of HPβCD with either Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate and efficiency of etoricoxib tablets. Direct compression method was more suitable to prepare etoricoxib tablets with rapid disintegration and dissolution characteristics employing drug- HPβCD - Poloxamer 407 / PVP K30 inclusion complexes.

Key words: Etoricoxib Tablets, HPβ Cyclodextrin, Poloxamer 407, PVP K30, Dissolution.

INRODUCTION

Etoricoxib, a widely prescribed anti diabetic drug belongs 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 the solubility and dissolution rate for increasing its oral bioavailability. Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrincomplexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, micro emulsion and self-emulsifying systems are available to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS Class II drugs[1]. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) 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[2,3]. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[4,5]. Poloxamer 407 is a polyethylene oxide- polypropylene oxide- polyethylene oxide triblock co-polymer of non-ionic nature and is used as a solubilising agent[6-8].

We reported[9] earlier that combination of cyclodextrins (βCD and HPβCD) with Poloxamer 407 and PVP K30 or Poloxamer 407 and PVP K30 alone have markedly enhanced the solubility and dissolution rate of etoricoxib, a BCS class II drug than is possible with them individually.

The objective of the present study is to evaluate the feasibility of formulating etoricoxib – HPβCD– Poloxamer 407 and etoricoxib – HPβCD –PVP K30 inclusion complexes into tablets and to evaluate the effects of HPβCD, Poloxamer 407 and PVP K30 on the dissolution rate of etoricoxib tablets in a 2^3 factorial study. Two methods i.e. wet granulation and direct compression methods were tried for the preparation of etoricoxib tablets employing etoricoxib- HPβCD-Poloxamer 407 and etoricoxib- HPβCD- PVP K30 inclusion complexes. A comparative evaluation of the two methods of preparation was also made.

MATERIALS AND METHODS

Etoricoxib was a gift sample from M/s NatcoPharma Ltd., Hyderabad. Crospovidone and poly vinyl pyrrolidone (PVP K30) were gift samples from M/s Dr. Reddy Laboratories, Hyderabad. Hydroxy propyl β- Cyclodextrin was gift sample from M/s. Cerestar Inc., USA. Methanol (Qualigens) and Poloxamer 407, lactose IP, talc and magnesium stearate were procured from commercial sources.

Estimation of Etoricoxib

A UV Spectrophotometric method based on the measurement of absorbance at 289 nm in phosphate buffer of pH 7.4 was used for the estimation of etoricoxib. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be0.68% and 1.02% respectively. No interference by the excipients used in the study was observed.

Preparation of Etoricoxib- HPβCD- Poloxamer 407/ PVP K30 Complexes

Solid inclusion complexes of etoricoxib, HPβCD, Poloxamer 407 and PVP K30 were prepared as per 2^3 – factorial study by kneading method. Etoricoxib, HPβCD, Poloxamer 407 and PVP K30 were triturated in a mortar with a small volume of solvent consisting of a blend of water: methanol (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55°C until dry. The dried mass was powdered and sieved to mesh No. 120.

Preparation of Etoricoxib- HPβCD - Poloxamer 407/ PVP K30Tablets

Compressed tablets each containing 60 mg of etoricoxib were prepared as per 2^3 – factorial study by (i) wet granulation and (ii) direct compression methods employing Etoricoxib- HPβCD - Poloxamer 407/ PVP K30 inclusion complexes. The formulae of the tablets prepared are given in Table 1.

Preparation of Tablets by Wet Granulation Method

Lactose was used as filler. Crospovidone (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 required quantities of drug, drug- HPβCD- Poloxamer 407 - PVP inclusion complexes and lactose were mixed thoroughly in a mortar by following geometric dilution technique. Water was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60^0 C for 4 h. Dried granules were passed through mesh No. 16 to break aggregates. Crospovidone (5%) and lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a 16- station tablet punching machine (M/s Cadmach machineries Pvt. Ltd., Ahmedabad) to a hardness of 5- 6 kg/cm^2 using 9 mm flat punches. In each case 100 tablets were compressed.

Table 1: Formulae of Etoricoxib Tablets Prepared by Wet Granulation and Direct Compression MethodsEmploying Drug- HPβCD – Poloxamer 407- PVP K30 Inclusion Complexes as per 2^3 Factorial Studies.

Ingredient (mg / tablet)	Etoricoxib Tablet Formulation*							
	WT_1 / DT_1	WT_a / DT_a	WT_b / DT_b	WT_{ab}/ DT_{ab}	WT_c / DT_c	WT_{ac} / DT_{ac}	WT_{bc}/ DT_{bc}	WT_{abc}/ DT_{abc}
Etoricoxib (1)**	60.0	-	-	-	-	-	-	-
Et - HPβCD (1:2) (a)	-	180.0	-	-	-	-	-	-
Et - P 407(2%) (b)	-	-	61.2	-	-	-	-	-
Et - HPβCD (1:2) - P 407(2%) (ab)	-	-	-	183.6	-	-	-	-
Et - PVP K30 (2%) (c)	-	-	-	-	61.2	-	-	-
Et - HPβCD (1:2) - PVP K30 (2%) (ac)	-	-	-	-	-	183.6	-	-
Et - P 407(2%) - PVP K30 (2%) (bc)	-	-	-	-	-	-	62.4	-
Et - HPβCD (1:2) - P 407 (2%) - PVP K30 (2%) (abc)	-	-	-	-	-	-	-	187.2
Crospovidone	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0
Talc	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Magnesium Stearate	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Lactose	140.2	20.1	139.0	16.6	139.0	16.6	137.8	13.0
Total weight	**220.0**	**220.0**	**220.0**	**220.0**	**220.0**	**220.0**	**220.0**	**220.0**

***W: Wet Granulation Method; D: Direct Compression Method; Et: Etoricoxib; HPβCD: Hydroxy propyl β cyclodextrin; P 407: Poloxamer 407; PVP K30: poly vinyl pyrrolidone K30; ** Figures in parentheses are codes as per 2^3 Factorial Design**.

Preparation of Tablets by Direct Compression Method

All the materials required as per the formulae were blended in a closed polyethylene bag. The blends were directly compressed into tablets on a 16- station tablet punching machine (M/s Cadmach machineries Pvt. Ltd., Ahmedabad) to a hardness of 5- 6 kg/cm^2 using 9 mm flat punches. In each case 100 tablets were compressed.

Evaluation of Tablets

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets prepared was determined using a Thermonic tablet disintegration test machine using water as test fluid.

Dissolution Rate Study

The dissolution rate of etoricoxib tablets prepared was studied in phosphate buffer of pH 7.4 at 289 nm using Disso 2000 (Labindia), 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±1°C was maintained throughout the study. One tablet containing 60 mg of etoricoxib was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed at 289 nm for etoricoxib. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

Analysis of Results

Dissolution data were subjected to analysis as per zero order and first order kinetics and the corresponding dissolution rates were calculated. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[10].

RESULTS AND DISCUSSION

The etoricoxib- HPβCD- Poloxamer 407 / PVP K30 inclusion complexes as per 2^3 factorial design were prepared by kneading method with a view to enhance the solubility and dissolution rate of etoricoxib, a BCS class II drug. All the solid inclusion complexes of Drug- HPβCD- Poloxamer 407 / PVP K30 prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v) values (< 1%) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate characteristics of these HPβCD- Poloxamer 407 / PVP K30 inclusion complexes were reported[9] earlier.

The feasibility of formulating etoricoxib- HPβCD - Poloxamer 407/ PVP K30 solid inclusion complexes into tablets was evaluated by preparing etoricoxib tablets employing the solid inclusion complexes by wet granulation and direct compression methods. To evaluate the individual and combined effects of HPβCD, Poloxamer 407 and PVP K30 on the dissolution rate and efficiency of etoricoxib tablets, tablets each containing 60 mg of etoricoxib were formulated employing solid inclusion complexes of drug- HPβCD - Poloxamer 407/ PVP K30 as per 2^3 factorial design. For this purpose two levels of HPβCD (0 and 1: 2 ratio of Drug : HPβCD) and two levels of each of Poloxamer 407 and PVP K30 (0 and 2%) were selected and the corresponding eight treatments involved in the formulation of tablets as per 2^3-factorial study were etoricoxib pure drug (1); Et - HPβCD (1:2) inclusion binary complex (a); Et - Poloxamer 407 (2%) binary mixture (b); Et- HPβCD (1:2) – Poloxamer 407 (2%) ternary complex (ab); Et – PVP K30 (2%) binary mixture (c); Et- HPβCD (1:2) – PVP K30 (2%) ternary complex (ac); Et – Poloxamer 407

(2%) - PVP K30 (2%) ternary complex (bc); Et- HPβCD (1:2)- Poloxamer 407 (2%) - PVP K30 (2%) inclusion complex (abc). The formulae of etoricoxib tablets prepared as per 2^3 factorial designemploying the above mentioned cyclodextrin inclusion complexes are given in Table 1. All the prepared tablets were evaluated for drug content, hardness, friability and disintegration time and dissolution rate of etoricoxib. The physical properties of the tablets prepared are given in Tables 2-3 and the dissolution parameters of the tablets prepared are summarised in Table 4.

Table 2: Physical Properties of Etoricoxib Tablets PreparedEmploying Drug- HPβCD – Poloxamer 407/ PVP K30 by Wet Granulation Method as per 2^3 Factorial Study.

Formulation code as per 2^3 factorial design	Hardness (Kg/sq. cm)	Friability (% weight loss)	DT (min-sec)	Drug Content (mg/tablet)
WT_1	4.5	0.65	0-52	60.5
WT_a	6.0	0.64	11-48	60.3
WT_b	5.5	0.84	02-48	59.7
WT_{ab}	5.5	0.83	05-36	60.1
WT_c	5.0	0.78	06-51	60.4
WT_{ac}	6.0	0.72	08-09	59.7
WT_{bc}	6.0	0.90	04-24	59.9
WT_{abc}	6.0	0.81	09-27	60.0

Table 3: Physical Properties of Etoricoxib Tablets PreparedEmploying Drug-HPβCD – Poloxamer 407/ PVP K30 by Direct Compression Method as per 2^3 Factorial Study.

Formulation code as per 2^3 factorial design	Hardness (Kg/sq. cm)	Friability (% weight loss)	DT (min-sec)	Drug Content (mg/tablet)
DT_1	4.5	0.85	0-05	59.7
DT_a	5.5	0.91	08-20	60.2
DT_b	5.0	0.87	0-10	59.5
DT_{ab}	5.0	0.85	03-13	60.3
DT_c	6.0	0.88	01-00	60.1
DT_{ac}	5.5	0.81	04-14	59.4
DT_{bc}	5.5	0.85	01-00	60.4
DT_{abc}	5.5	0.79	06-21	59.5

Table 4: Dissolution Parameters of Etoricoxib Tablets PreparedEmploying Drug- HPβCD – Poloxamer 407/ PVP K30 Inclusion Complexes by Wet Granulation and Direct Compression Methods as per 2^3 Factorial Study

Formulation code as per 2^3 factorial design	Wet Granulation Method				Direct Compression Method			
	T_{50} (min)	Dissolution Rate ($K_1 \times 10^2$) (min^1) ($x \pm s.\bar{d}.$)	Increase in K_1 (no. of folds)	Dissolution Efficiency (DE_{30})(%) ($x \pm s.\bar{d}$)	T_{50} (min)	Dissolution Rate ($K_1 \times 10^2$) (min^{-1}) ($x \pm s.\bar{d}$)	Increase in K_1 (no. of folds)	Dissolution Efficiency (DE_{30})(%) ($x \pm s.\bar{d}$)
T_1	>60	0.57±0.010	-	7.26±0.262	50	1.02±0.040	-	21.74±0.456
T_a	>60	0.49±0.006	0.85	5.48±0.155	19	2.40±0.0.091	2.35	32.87±0.858
T_b	14	2.69±0.015	4.73	45.05±0.398	05	4.61±0.357	4.51	65.75±0.404
T_{ab}	09	3.15±0.182	5.53	58.69±0.513	10	4.48±0.165	4.38	55.60±0.371
T_c	30	1.54±0.082	2.70	31.08±0.757	10	3.31±0.156	3.23	52.68±1.068
T_{ac}	>60	0.43±0.000	0.75	8.66±0.084	23	2.66±0.076	2.60	31.49±0.947
T_{bc}	25	1.98±0.078	3.48	33.52±0.999	03	6.23±0.261	6.09	72.68±1.104
T_{abc}	26	2.15±0.031	3.77	30.66±0.856	12	3.40±0.079	3.32	50.91±0.557

All the tablets prepared were found to contain etoricoxib within 100±5% of the labelled claim. Hardness of the tablets was in the range 4.5- 6.0 Kg/cm^2. Percentage weight loss in the friability test was less than 0.98% in all the cases. In both wet granulation and direct compression method plain tablets formulated employing etoricoxib alone disintegrated within 1 min. The tablets prepared by direct compression method employing drug- Poloxamer 407, drug- PVP K30 and drug- Poloxamer 407 – PVP K30 complexes also disintegrated rapidly within 1 min. All the formulations prepared by direct compression method employing HPβCD containing complexes disintegrated slowly in 3 – 9 min. All tablets prepared by wet granulation method employing HPβCD– Poloxamer 407/ PVP K30 inclusion complexes disintegrated slowly and the disintegration times of these tablets were in the range 2- 12 min. However all the tablets prepared employing HPβCD– Poloxamer 407/ PVP K30 inclusion complexes by both wet granulation and direct compression methods fulfilled the official (I.P) disintegration time specification of uncoated tablets.The dissolution rate of etoricoxib from the tablets prepared was studied in 900 ml of phosphate buffer of pH 7.4.

Dissolution of etoricoxib from all the tablets prepared followed first order kinetics. The correlation coefficient (r) values were higher in the first order model than those in the zero order model in all the cases. The dissolution parameters (T_{90}, K_1 and DE_{30}) of various tablets are summarized in Table 4.

Etoricoxib dissolution was rapid and higher from the tablets formulated employing drug- HPβCD- Poloxamer 407/ PVP K30 inclusion complexes when compared to the tablets containing etoricoxib alone in both wet granulation and direct compression methods. Dissolution parameters, K_1 and DE_{30} in each case were subjected to ANOVA to find out the significance of the individual and combined effects of the three factors (HPβCD, Poloxamer 407, PVP K30) in enhancing the dissolution rate and efficiency of etoricoxib tablets. The individual as well as combined effects of the three factors involved i.e., HPβCD (factor A), Poloxamer 407 (factor B) and PVP K30 (factor C) were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of etoricoxib in both wet granulation and direct compression methods. Among the three factors Poloxamer 407

(factor B) gave highest enhancement in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of etoricoxib tablets in both wet granulation and direct compression methods.

HPβCD alone gave a dissolution rate (K_1) of 0.49 x 10^{-2} and 2.40 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. Whereas HPβCD in combination with Poloxamer 407 gave a dissolution rate (K_1) of 3.15 x 10^{-2} and 4.48 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. Similarly HPβCD in combination with PVP K30 gave a dissolution rate (K_1) of 0.43 x 10^{-2} and 2.66 x 10^{-2} min^{-1} respectively in the wet granulation and direct compression methods. Thus combination of HPβCD with Poloxamer 407 gave a significantly higher dissolution rate (K_1) of etoricoxib in both wet granulation and direct compression methods. Combination of HPβCD with PVP K30 also gave a significantly higher dissolution rate (K_1) of etoricoxib in the direct compression method. Overall direct compression method gave higher dissolution rates (K_1) and dissolution efficiency (DE_{30}) values than the wet granulation method in all the cases. Hence Poloxamer 407 alone or a combination of HPβCD with either Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate and efficiency of etoricoxib tablets. Direct compression method was found more suitable to prepare etoricoxib tablets with rapid disintegration and dissolution characteristics employing drug- HPβCD - Poloxamer 407 / PVP K30 inclusion complexes.

CONCLUSION

Etoricoxib tablets formulated employing drug – HPβCD – Poloxamer 407 / PVP K30 inclusion complexes and prepared by direct compression method disintegrated rapidly when compared to those made by wet granulation method. Etoricoxib dissolution was rapid and higher from the tablets formulated employing drug- HPβCD- Poloxamer 407/ PVP K30 inclusion complexes when compared to the tablets containing etoricoxib alone in both wet granulation and direct compression methods. The individual as well as combined effects of the three factors involved i.e., HPβCD (factor A), Poloxamer 407 (factor B) and PVP K30 (factor C) were highly significant ($P< 0.01$) in enhancing the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of etoricoxib in both wet granulation and direct compression methods. Among the three factors Poloxamer 407 (factor B) gave highest enhancement in the dissolution rate (K_1) and dissolution efficiency (DE_{30}) of etoricoxib tablets in both wet granulation and direct compression methods. HPβCD alone gave low dissolution rates in both wet granulation and direct compression methods.

Combination of HPβCD with Poloxamer 407 gave a significantly higher dissolution rate (K_1) of etoricoxib in both wet granulation and direct compression methods. Combination of HPβCD with PVP K30 also gave a significantly higher dissolution rate (K_1) of pioglitazone in the direct compression method. Overall direct compression method gave higher dissolution rates (K_1) and dissolution efficiency (DE_{30}) values than the wet granulation method in all the cases.

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