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Formulation and Evaluation of Nimesulide Tablets Employing Cyclodextrin-Poloxamer 407- PVP K30 Inclusion Complexes

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ABSTRACT

Nimesulide, an 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 Nimesulide – CD (βCD/ HPβCD) – Poloxamer 407 and nimesulide – CD (βCD/ HPβCD) –PVP K30 inclusion complexes into tablets and to evaluate the effects of CDs, Poloxamer 407 and PVP K30 on the dissolution rate of nimesulide tablets. A comparative evaluation of wet granulation and direct compression methods was made for the preparation of tablets employing drug – CD – Poloxamer 407 / PVP K30 inclusion complexes. Drug – CD- Poloxamer 407 / PVP K30 inclusion complexes were prepared by kneading method. Tablets each containing 50 mg of nimesulide were prepared by wet granulation and direct compression methods employing various CD complexes and the tablets were evaluated for dissolution rate and other physical properties. In both wet granulation and direct compression methods tablets formulated employing βCD complexes disintegrated relatively more rapidly than those formulated employing HP βCD complexes. Tablets formulated employing HP βCD complexes and prepared by wet granulation method did not fulfil the official (I.P.) disintegration test specification of uncoated tablets. The wet granulation method gave higher dissolution rates in the case of βCD complexes when compared to direct compression method. Tablets formulated employing drug – βCD, drug- βCD- Poloxamer 407 and drug- βCD- PVP K30 gave respectively 7.14, 6.67 and 4.57 fold increases in the dissolution rate of nimesulide when compared to plain tablets in wet granulation method. Hence βCD alone and in combination with Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate of nimesulide tablets. Wet granulation method was found more suitable for the preparation of tablets employing drug- βCD and drug- βCD- Poloxamer 407/ PVP K30 complexes.

Key words: Nimesulide Tablets, β Cyclodextrin, HP β Cyclodextrin, Poloxamer 407, PVP K30, Dissolution Rate.

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INTRODUCTION

Nimesulide, an anti- inflammatory 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 cyclodextrin complexation, 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 either Poloxamer 407 or PVP K30 has markedly enhanced the solubility and dissolution rate of nimesulide, a BCS class II drug than is possible with them individually. The objective of the present study is to evaluate the feasibility of formulating nimesulide – CD (βCD/ HPβCD) – Poloxamer 407 and nimesulide – CD (βCD/ HPβCD) –PVP K30 inclusion complexes into tablets and to evaluate the effects of CDs, Poloxamer 407 and PVP K30 on the dissolution rate of nimesulide tablets. Two methods i.e. wet granulation and direct compression methods were tried for the preparation of nimesulide tablets employing nimesulide- CD- Poloxamer 407 and nimesulide- CD- PVP inclusion complexes. A comparative evaluation of the two methods of preparation was also made.

MATERIALS AND METHODS

Materials

Nimesulide, crosspovidone and poly vinyl pyrrolidone (PVP K30) were gift samples from M/s Dr. Reddy Laboratories, Hyderabad. β- Cyclodextrin and HP β- Cyclodextrin were gift samples from M/s. Cerestar Inc., USA. Methanol (Qualigens) and Poloxamer 407, lactose IP, talc and magnesium stearate were procured from commercial sources.

Estimation of Nimesulide

A UV Spectrophotometric method based on the measurement of absorbance at 397 nm in alkaline borate buffer of pH 8.4 was used for the estimation of nimesulide. 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 be 0.80% and 1.20% respectively. No interference by the excipients used in the study was observed.

Preparation of Drug-CD- Poloxamer 407/ PVP K30 Complexes

Solid inclusion complexes of nimesulide- βCD (1:2), nimesulide- βCD(1:2)- Poloxamer 407 (2%), nimesulide- βCD(1:2)- PVP K30 (2%), nimesulide- HPβCD (1:2), nimesulide- HPβCD(1:2)- Poloxamer 407 (2%), nimesulide- HPβCD(1:2)- PVP K30 (2%), were prepared by kneading method. Nimesulide, βCD and Poloxamer 407/ 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^{o}C until dry. The dried mass was powdered and sieved to mesh No. 120.

Preparation of Nimesulide- CD - Poloxamer 407/ PVP K30 Tablets

Compressed tablets each containing 50 mg of nimesulide were prepared by (i) wet granulation and (ii) direct compression methods employing Nimesulide- CD - Poloxamer 407/ PVP K30 inclusion complexes as per the formulae given in Table 1

Table 1: Formulae of Nimesulide Tablets Prepared by Wet Granulation and Direct Compression Methods Employing Drug- CD – Poloxamer 407/ PVP K30 Inclusion Complexes

Ingredient (mg / tablet)	Nimesulide Tablet Formulation*						
	WT1/ DT1	WT2/ DT2	WT3/ DT3	WT4/ DT4	WT5/ DT5	WT6/ DT6	WT7/ DT7
Nimesulide	50	-	-	-	-	-	-
Nim - βCD (1:2)	-	150	-	-	-	-	-
Nim - βCD - P 407(2%)	-	-	153	-	-	-	-
Nim - βCD - PVP (2%)	-	-	-	153	-	-	-
Nim - HPβCD (1:2)	-	-	-	-	150	-	-
Nim - HPβCD - P 407 (2%)	-	-	-	-	-	153	-
Nim - HPβCD - PVP (2%)	-	-	-	-	-	-	153
Cross Povidone	11	11	11	11	11	11	11
Talc	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
Lactose	160.2	50.2	47.2	47.2	50.2	47.2	47.2
Total weight	220	220	220	220	220	220	220

* W: Wet Granulation Method; D: Direct Compression Method; Nim: Nimesulide; P 407: Poloxamer 407; PVP: poly vinyl pyrrolidone.

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Preparation of Tablets by Wet Granulation Method

Lactose was used as filler. Crosspovidone (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 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.

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 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 nimesulide tablets prepared was studied in alkaline borate buffer of pH 8.4 (900 ml) using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±1^{o}C was maintained throughout the study. One tablet containing 50 mg of nimesulide 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 397 nm for nimesulide. 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 nimesulide- CD- Poloxamer 407 / PVP K30 complexes were prepared by kneading method. All the solid inclusion complexes of Drug- CD- 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 feasibility of formulating nimesulide- CD - Poloxamer 407/ PVP K30 solid inclusion complexes into tablets was evaluated by preparing nimesulide tablets employing the solid inclusion complexes by wet granulation and direct compression methods. The formulae of nimesulide tablets prepared are given in Table 1. All the prepared tablets were evaluated for drug content, hardness, friability and disintegration time and dissolution rate of nimesulide. 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 Nimesulide Tablets Prepared by Wet Granulation Method

Formulation	Hardness (Kg/cm^2)	Friability (% weight loss)	Disintegration Time (min-sec)	Drug Content (mg/tablet)
WT1	5.0	0.86	0-45	49.5
WT2	5.0	0.90	0-33	50.0
WT3	4.5	0.88	3-21	51.2
WT4	5.0	0.79	4-37	49.6
WT5	6.0	0.64	17-35	50.0
WT6	5.5	0.73	16-34	50.5
WT7	6.0	0.89	16-20	49.8

Table 3: Physical Properties of Nimesulide Tablets Prepared by Direct Compression Method

Formulation	Hardness (Kg/cm^2)	Friability (% weight loss)	Disintegration Time (min-sec)	Drug Content (mg/tablet)
DT1	5.5	0.90	0-13	50.0
DT2	5.0	0.88	1-32	49.8
DT3	4.5	0.84	3-06	50.4
DT4	6.0	0.75	7-48	50.7
DT5	5.5	0.82	7-49	49.8
DT6	6.0	0.77	8-22	51.2
DT7	6.5	0.92	9-12	49.6

Table 4: Dissolution Parameters of Nimesulide Tablets Prepared by Wet Granulation and Direct Compression Methods

Formulation	Wet Granulation Method		Direct Compression Method	
	Dissolution Rate ($K_1 \times 10^2$) (min^1) ($x \pm \bar{} $ s.d.)	Dissolution Efficiency (DE_{30}) (%) ($x \pm$ s.d.) $\bar{}$	Dissolution Rate ($K_1 \times 10^2$) (min^1) ($x \pm \bar{} $ s.d.)	Dissolution Efficiency (DE_{30}) (%) ($x \pm$ s.d.) $\bar{}$
T1	2.01 ± 0.02	17.79 ± 0.13	2.40 ± 0.003	21.01 ± 0.22
T2	14.35 ± 0.24	41.22 ± 0.16	8.60 ± 0.17	34.72 ± 0.31
T3	13.40 ± 0.38	38.56 ± 0.39	8.81 ± 0.01	32.74 ± 0.15
T4	9.18 ± 0.48	38.21 ± 0.11	7.14 ± 0.15	32.63 ± 0.17
T5	1.73 ± 0.02	8.19 ± 0.01	9.29 ± 0.12	25.11 ± 0.26
T6	1.68 ± 0.01	7.40 ± 0.03	8.42 ± 0.03	31.49 ± 0.06
T7	1.90 ± 0.02	10.26 ± 0.01	5.88 ± 0.11	24.83 ± 0.20

All the tablets prepared were found to contain nimesulide within 100±5% of the labelled claim. Hardness of the tablets was in the range 4.5- 6.5 Kg/cm^2. Percentage weight loss in the friability test was less than 0.92% in all the cases. In both wet granulation and direct compression method plain tablets formulated employing nimesulide alone disintegrated within 1 min. In the wet granulation method tablets formulated employing βCD complexes disintegrated rapidly with in 4.0 min whereas tablets formulated employing HP βCD complexes disintegrated slowly and the disintegration times of these tablets were in the range 16 – 18 min. In the direct compression method all the tablets formulated employing βCD and HP βCD complexes disintegrated within 1- 10 min. In both the methods tablets formulated employing βCD complexes disintegrated relatively more rapidly than those formulated employing HP βCD complexes.

The dissolution rate of nimesulide from the tablets prepared was studied in 900 ml of alkaline borate buffer of pH 8.4. Dissolution of nimesulide from all the tablets prepared followed first order kinetics with r (correlation coefficient) above 0.9106. The dissolution parameters (K_1 and DE_{30}) of various tablets are summarized in Table 4. In the case of wet granulation method tablets formulated employing βCD complexes (WT2, WT3, WT4) gave higher dissolution rates (K_1) and DE_{30} values than the plain tablets (WT1) and tablets formulated employing HP βCD complexes (WT5, WT6, WT7). In the case of direct compression method all the tablets formulated employing βCD and HP βCD complexes gave higher dissolution rates (K_1) and DE_{30} values than the plain tablets.

Tablets formulated employing drug – βCD (WT2), drug- βCD- Poloxamer 407 (WT3) and drug- βCD- PVP K30 (WT4) gave respectively 7.14, 6.67 and 4.57 fold increases in the dissolution rate of nimesulide when compared to plain tablets in wet granulation method. Whereas in the case of direct compression method they respectively gave 3.58, 3.67 and 2.97 fold increase in the dissolution rate of nimesulide when compared to the corresponding plain tablets. The wet granulation method gave higher dissolution rates in the case of βCD complexes when compared to direct compression method. Whereas in the case of HP βCD complexes direct compression method gave higher dissolution rates than wet granulation method. Overall tablets formulated employing drug- βCD and drug- βCD- Poloxamer 407/ PVP K30 complexes and prepared by wet granulation method gave higher dissolution rates (K_1) and DE_{30} values.
Hence βCD alone and in combination with Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate of nimesulide tablets. Wet granulation method was found more suitable for the preparation of tablets employing drug- βCD and drug- βCD- Poloxamer 407/PVP K30 complexes.

CONCLUSION

In both wet granulation and direct compression methods tablets formulated employing βCD complexes disintegrated relatively more rapidly than those formulated employing HP βCD complexes. Tablets formulated employing HP βCD complexes and prepared by wet granulation method did not fulfil the official (I.P.) disintegration test specification of uncoated tablets. The

wet granulation method gave higher dissolution rates in the case of βCD complexes when compared to direct compression method. Tablets formulated employing drug – βCD, drug- βCD- Poloxamer 407 and drug- βCD- PVP K30 gave respectively 7.14, 6.67 and 4.57 fold increases in the dissolution rate of nimesulide when compared to plain tablets in wet granulation method. Hence βCD alone and in combination with Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate of Nimesulide tablets. Wet granulation method was found more suitable for the preparation of tablets employing drug- βCD and drug- βCD- Poloxamer 407/ PVP K30 complexes.

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