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Original Article

Effect of β-CD and superdisintegrant levels on formulation development of Amlodipine IR tablets as per 2^2 factorial design

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ABSTRACT

Amlodipine, a widely prescribed anti-hypertensive drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It needs enhancement in the dissolution rate in its formulation development. Complexation with β-cyclodextrin (βCD) and use of superdisintegrant (Primojel) are tried for enhancing the dissolution rate of Amlodipine tablets. The objective of the present study is to study the effect of βCD and superdisintegrant levels for formulation of Amlodipine IR tablets by 2^2 factorial design to achieve NLT 80% dissolution in 30min. A total of four Amlodipine IR tablet formulations were prepared using selected combinations of the two factors as per 2^2 factorial design. Amlodipine tablets were prepared by direct compression method and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K1) values were analysed as per ANOVA of 2^2 factorial design to find the significance of the individual and combined effects of the two factors (βCD and superdisintegrant) involved on the dissolution rate of Amlodipine tablets formulated. The individual and combined effects of βCD (1:1 and 1:5 ratio of drug content) and Primojel (2% and 30% of drug content) on the dissolution rate (K1) of Amlodipine tablets are highly significant ($P<0.01$). Amlodipine tablets formulated employing Primojel at a level of 30% of drug content and βCD in 1:5 ratio of drug: βCD (F_{ab}) disintegrated rapidly within 20 seconds and gave very rapid dissolution of Amlodipine fulfilling the target dissolution of NLT 80% in 30 min. Higher levels of βCD lower levels of superdisintegrants gave low dissolution rates. βCD in 1:5 ratio of drug: βCD and superdisintegrant (Primojel) at a level of 30% of drug content are the optimized levels for formulation of Amlodipine IR tablets to obtain the dissolution of NLT 80% in 30 min

INTRODUCTION

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters. These BCS class II drugs pose challenging problems in their pharmaceutical product development process. Amlodipine, a widely prescribed anti-hypertensive drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility.

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Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. It needs enhancement in the dissolution rate in its formulation development. Several techniques [1] such as micronisation, cyclodextrin-complexation, use of surfactants, solubilizers and super disintegrants, solid dispersion in water soluble and water dispersible carriers, microemulsions and self-emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS class II drugs. Among the various approaches cyclodextrin complexation [2], [3] and use of superdisintegrant [4],[5] such as sodium starch glycolate (primojel) are simple industrially useful approaches for enhancing the dissolution rate of poorly soluble drugs in their formulation development. The objective of the present study is to study the effect of βCD and superdisintegrant levels in formulation of Amlodipine IR tablets by 2^2 factorial design to achieve NLT 80% dissolution in 30min.

MATERIALS AND METHODS

Materials

Amlodipine was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. B-cyclodextrin, and Primojel were gift samples from M/s. Nalco Pharma Ltd., Hyderabad. Talc and magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods

Estimation of Amlodipine[6]

An UV Spectrophotometric method based on the measurement of absorbance at 239nm in 0.01N hydrochloric acid was used for the estimation of Amlodipine. 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 0.92% and 1.65% respectively. No interference by the excipients used in the study was observed.

Formulation of Amlodipine Tablets

For Formulation of Amlodipine IR tablets as per 2^2 factorial design, βCD and superdisintegrant (primojel) are considered as the two factors. The two levels of the factor A superdisintegrant(Primojel) are 2% and 30% of drug content and the two levels of the factor B (βCD) are 1:1 and 1:5 ratio of drug: βCD. Four Amlodipine IR tablet formulations employing selected combinations of the two factors i.e., Superdisintegrant and βCD as per 2^2 factorial design were formulated and prepared by direct compression method.

Preparation of Amlodipine Tablets

Amlodipine tablets were prepared by direct compression method as per the formula given in Table 1.The required quantities of Amlodipine, βCD and superdisintegrant (primojel) as per the formula in each case were blended thoroughly in a closed polythene bag. Talc and magnesium stearate were then added by passing through mesh no.80 and blended.The blend of ingredients was compressed directly into tablets using an 8-station RIMEK tablet punching machine employing 9mm or 12mm round and flat punches.

Evaluation of Tablets

All the Amlodipine tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows:

Hardness

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm2.

Friability

The friability of the tablets was measured in a Roche friabilator using the formula

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Drug Content

Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of Amlodipine was taken into 100 ml volumetric flask, dissolved in 0.01N Hydrochloric acid and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with 0.01N hydrochloric acid and assayed for Amlodipine at 239 nm.

Disintegration time

Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.

Dissolution Rate Study

Dissolution rate of Amlodipine tablets prepared was studied in 0.01N hydrochloric acid (900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for Amlodipine at 239 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times. Each dissolution experiment was run in triplicate (n=3).

Analysis of Data

The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE_{30}) values were estimated as suggested by Khan[7][8]. Dissolution rate (K_1) values were analyzed as per ANOVA of 2^2 factorial experiments.

Table 1. Formulae of Amlodipine Tablets Prepared as Per 2^2 Factorial Design employing βCD and Primojel

FORMULATION	F_1	F_a	F_b	F_{ab}
Amlodipine	100mg	100mg	100mg	100mg
Beta-cyclodextrin	100mg	100mg	500mg	500mg
Primojel	2mg	30mg	2mg	30mg
Talc	4mg	4.6mg	12mg	12.6mg
Magnesium stearate	4mg	4.6mg	12mg	12.6mg
Total	**210mg**	**239.2mg**	**626mg**	**642.6mg**

Table 2. Physical Parameters of AmlodipineTablets Prepared as per 2^2 Factorial Design employing βCD and Primojel

Formulation	Hardness (Kg/Cm^2)	Friability (% Wt Loss)	Disintegration time(Min-sec)	Drug content (mg/tablet)
F_1	5.0	0.78	8-50	98.8
F_a	5.0	0.67	0-30	99.0
F_b	4.5	0.93	5-50	98.8
F_{ab}	4.5	0.88	0-20	98.7

Table 3. Dissolution Parameters of Amlodipine Tablets Prepared as per 2^2 Factorial Design employing βCD and Primojel

Formulation	PD_{15} (%)	T_{50} (min)	T_{90} (min)	DE_{30} (%) ($\bar{x} \pm$ sd)	$K_1 X 10^3$ (min^{-1}) ($\bar{x} \pm$ s d)	Official specification
F_1	30.08	25	>60	31.16±0.47	38±0.52	NLT 70% dissolution in 45mins
F_a	49.09	17	40	40.88±0.94	58.5±8.61	
F_b	32.83	20	50	35.84±0.81	43±1.88	
F_{ab}	63.9	13	39	55.52±0.47	61±1.24	

Table 4. ANOVA of Dissolution rates (K1) of Amlodipine tablets Prepared using βCD and Primojel as per 2^2 factorial design

Source of variation	DF	SS	MSS	F-ratio
Total	11	73833		
Treatment	3	73734	24578	1.9869
Error	8	99	12.37	
F_a	1	17480	17480	1413.0
F_b	1	14008.3	14008.3	1132.4
F_{ab}	1	42245.3	42245.3	3415.14

RESULTS

The objective of the present study is to study the effect of β-CD and super disintegrant on formulation and enhancement of dissolution rate of amlodipine IR tablets as per 2^2 Factorial design. According to 2^2 Factorial design, β-CD and Primojel are considered as two Factors. The two levels of the Factor A Superdisintegrant (primojel) are 2% and 30% of drug content and The two levels of the Factor B (β –CD) are 1:1 and 1:5 ratio of drug content; Four amlodipine tablet formulations employing selected combinations of the two Factors i.e. β-CD (1:1 and 1:5 ratio of drug content) and primojel (2% and 30% of drug content) as per 2^2 Factorial design were prepared. The tablets were prepared by direct compression method as per the formula given in table 1 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics.the dissolution rate (K1) values were analysed as per ANOVA of 2^2 Factorial design to find out the significance of the individual and combined effects of the two Factors involved on the dissolution rate of amlodipine tablets formulated. The physical parameters of the amlodipine tablets prepared are given in Table 2. The hardness of the tablets was in the range 4.5-5.0 kg/cm^2. Weight loss in the friability test was less than 0.95 % in all the cases. Amlodipine content of the tablets prepared was with in 100±3 %. Many variations were observed in the disintegration and dissolution characteristics of the amlodipine tablets prepared. The disintegration times were in the range 20 sec to 8min 50 sec . Amlodipine tablet formulations (F_{ab}) disintegrated rapidly with in 20 sec. All other tablets disintegrated rather slowly in about 40sec -9 min. As Primojel concentration is increased the disintegration time is reduced. However, all the amlodipine tablets prepared fulfilled the official (IP 2014) requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets. Dissolution rate of amlodipine tablets prepared was studied in 0.01N hydrochloric acid. The dissolution parameters are given in Table 3 and the dissolution profiles are shown in fig.1. Dissolution of amlodipine from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.962. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate (K_1) values of the tablets prepared due to formulation variables. ANOVA (Table – 4) of K_1 values indicated that the individual and combined effects of the two Factors, β – CD and Primojel in influencing the dissolution rate of amlodipine tablets are highly significant ($P < 0.01$). Amlodipine tablet formulations (F_{ab}) gave very rapid dissolution of amlodipine than others. These tablets (F_{ab}) gave 88.54% dissolution in 30min. Higher levels of β - CD and lower levels of Primojel gave low dissolution of amlodipine tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $F_{ab} > F_a > F_b > F_1$. Hence amlodipine tablets could be formulated employing β - CD and primojel as per 2^2

Factorial design to obtain desired target dissolution of NLT 80% dissolution in 30 min.

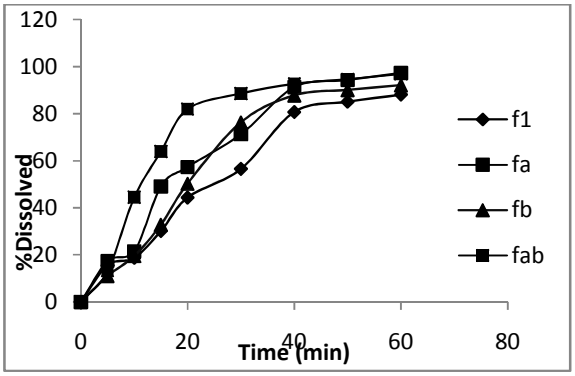

Figure 1. Dissolution Profiles of Amlodipine Tablets Prepared employing βCD and Primojel as per 2^2 Factorial Design

DISCUSSION

The individual and combined effects of β –CD (1:1 and 1:5 ratio of drug content) and Primojel (2% and 30% of drug content) on the dissolution rate (K1) of amlodipine tablets are highly significant (P<0.01). Amlodipine tablets formulated employing superdisintegrant (Primojel) at a level of 30% of drug content and β –CD at 1:5 ratio of drug content (F_{ab}) disintegrated rapidly within 20 seconds and gave very rapid dissolution of amlodipine fulfilling the target dissolution of NLT 80% in 30 min. The results indicated that β –CD at 1:5 ratio of drug content and superdisintegrant (Primojel) at a level of 30% of drug content are the optimized levels of β –CD and superdisintegrant for formulation of amlodipine IR tablets to obtain a dissolution of NLT 80% in 30 min. The increasing order of dissolution rate (K_1) observed with various formulations was $F_{ab} > F_a > F_b > F_1$.

The amlodipine tablet formulation F_{ab} prepared using β –CD at 1:5 ratio of drug content and (Primojel) at a level of 30% of drug content gave 88.54% dissolution in30 min fulfilling the target dissolution set of NLT 80% in 30 min. Hence amlodipine tablets can be formulated employing βCD and Primojel in order to enhance the dissolution rate as per 2^2 factorial design.

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