RESEARCH ARTICLE

Understanding Degradation Pathway of Poorly Stable Diltiazem Hydrochloride and Development of its Stabilized Controlled-release Tablets

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ABSTRACT

Diltiazem hydrochloride is a class -1 drug, as per the breast-conserving surgery (BCS) classification system, which is highly soluble and highly permeable. It is a poorly stable drug that poses many problems during formulation preparation. The stability of the final product is quite challenging. The API undergoes hydrolysis to form desacetyl-diltiazem. It is the major degradation impurity. Desacetyl-diltiazem exhibits only a quarter to half of the pharmacological activity as compared to diltiazem HCl. A correct understanding of the degradation pathway and usage of suitable excipients can provide a stable product with improved shelf life. During the course of various trials and application of factorial designing, an optimized composition for oral controlled release tablets of diltiazem HCl has arrived, suggesting that exposure to an aqueous medium for tablets granulation and eliminating the polyvinylpyrrolidone from the composition significantly improved the product stability and final tablets shelf life by not only maintaining the desired *in-vitro* drug release profile but also keeping the related substances (impurities level) at very low levels throughout the entire shelf life.

Keywords: Diltiazem hydrochloride, Controlled release, Hydrolysis, Desacetyl-diltiazem, Degradation, Related substance, Stability.

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INTRODUCTION

Diltiazem hydrochloride, which is a calcium ion cellular influx inhibitor (slow channel blocker or calcium antagonist), does provide therapeutic benefits mainly related to its ability to inhibit calcium ions influx during membrane depolarization of cardiac and vascular smooth muscle of cardiac and vascular system.[1]

Diltiazem HCl is predominantly used for the treatment of specific cardiovascular ailments. Its therapeutic impacts are associated with its capacity to lower the flood of calcium ions in cardiovascular and vascular smooth muscle, during membrane depolarization. Generally, a dose more than once a day improve compliance of the person under treatment.[2,3]

Diltiazem's therapeutic actions are mainly *via* following mechanism.[4,5]

- **Angina due to Coronary Artery Spasm:** Diltiazem is proven to be a potent dilator of coronary arteries (both epicardial and sub-endocardial). Spontaneous and ergonovine-induced coronary artery spasms are blocked by diltiazem HCl.
- **Exertional Angina:** Diltiazem HCl enhances exercise tolerance due to its ability to reduce myocardial oxygen demand. This is achieved primarily due to reductions in heart rate and systemic blood pressure at submaximal and maximal exercise workloads.

In animal models, diltiazem causes coronary vascular smooth muscle relaxation and dilation of both large and small coronary arteries at drug levels which causes small or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and sub-endocardial) happen in ischemic and non-ischemic models. This is accompanied

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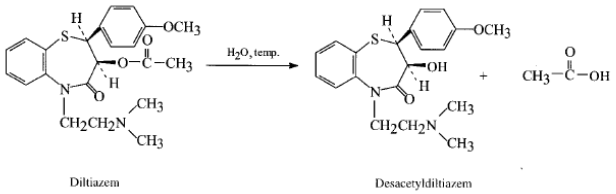

Figure 1: Degradation of diltiazem HCl to des-acetyl diltiazem

by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.[6]

Diltiazem HCl was found to undergo hydrolysis to desacetyl-diltiazem in the aqueous media (Figure 1). Desacetyl-diltiazem possesses just a quarter to half of the drug's pharmacological activity.[7-9]

The aim of the present study was to formulate a controlled release tablet of diltiazem hydrochloride with maximum stability and the lowest rate of hydrolysis.

Controlled release formulation maintains a uniform drug level in blood with improved patient compliance.[10] Prolonged-release tablets are taken more than once per day during a course of treatment, whereas in conventional drug delivery systems, it requires to take 3 to 4 times dose in a multi-day to achieve a similar therapeutic action.[11]

In this study, multiple formulation trials were taken using the excipients which are less prone to hydrolysis of API. Additionally, for establishing the stability of API, a trial was planned with the excipient which may help the hydrolysis of diltiazem HCl.

MATERIALS AND METHODS

Diltiazem HCl USP was procured from M/s Dr. Reddy Lab. Other excipients were procured from different vendors of excipients like from M/s signet etc.

Manufacturing Process

All the formulations were prepared according to Table 1. The diltiazem HCl, ethyl cellulose and hydroxyethyl cellulose polymer were blended uniformly in rapid mixer granulator. This dry mix blend was further granulated using either the binder solution of PVP k 30 in water or using IPA as per the formulation type. The wet granular mass was dried. The dried granules were passed through sieve number 16. The resulting granules were waxed using cetostearyl alcohol and conditioned for a sufficient time period to harden the waxed granules. These waxed granules were further sized using a suitable number of sieves to get desired granule size. These granules were lubricated talc, magnesium stearate and other remaining excipients. The lubricated blend was compressed into tablets using 9.0 mm round biconcave punch in 8 stations single rotary machine. Hardness was kept between the ranges of 3.0–6.0 kp.

Physical Character of the Tablets

Tablet weight variation test was performed as per the pharmacopoeial specifications (IP 2020). For tablet thickness, digital vernier calipers were used for testing. Dr. Sheluinger

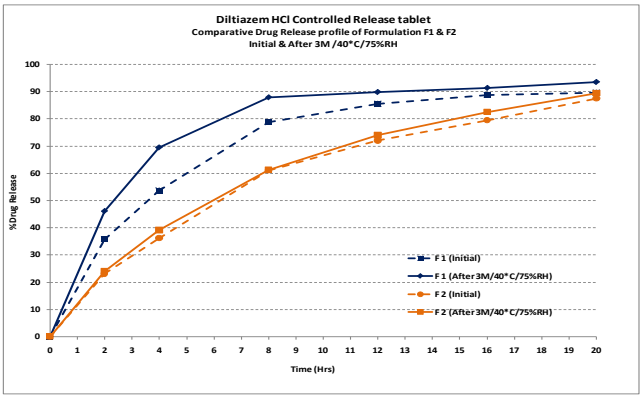

Figure 2: Cumulative drug release profile of diltiazem HCl CR tablet

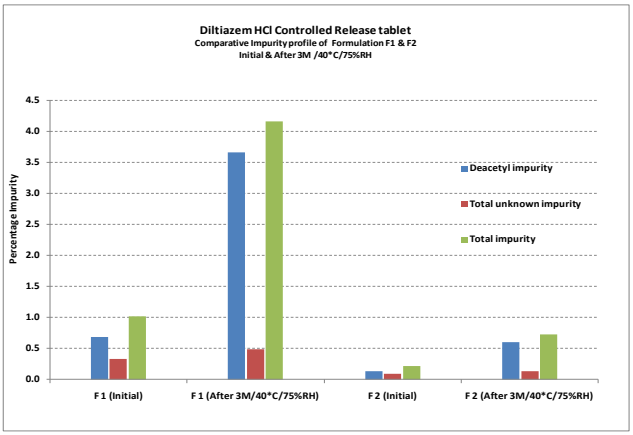

Figure 3: Impurity profile of diltiazem HCl CR tablet

hardness tester was used for tablet hardness measurements, and the electrolab friabilator tester was utilized for evaluating the friability of tablets.

Related Substance (Impurity)

For the formulation trials, USP grade diltiazem HCl was used. The USP monograph of API-diltiazem HCl had a broader limit of related substances. In the USP, a monograph for controlled release tablet of diltiazem HCl is not available. Therefore, the USP monograph for extended release capsule of diltiazem hydrochloride was considered for the determination of the impurity level in the formulation trials. Related substances were measured using high-pressure liquid chromatography (HPLC).

In-vitro Drug Dissolution

The drug dissolution profiles of diltiazem HCl tablets was tested using USP type-1 dissolution apparatus. *In-vitro* drug dissolution study was done in the 900 mL, pH 4.5 phosphate buffer medium at 100 rpm. The dissolution study was carried out up to 20 hours.

Stability Study

The finalized formulation of diltiazem HCl tablets was packed in aluminium strip and kept on accelerated stability conditions per ICH guideline.[12] Formulations were analyzed after three months by physicochemical methods.

Table 1: Different formulations of diltiazem hydrochloride Controlled-release Tablets

S.No.	*Ingredients*	*F1*	*F2*	*F3*	*F4*	*F5*
		Qty./tab(mg)	*Qty./tab (mg)*	*Qty./tab (mg)*	*Qty./tab (mg)*	*Qty./tab (mg)*
01	Diltiazem HCl	120.00	120.00	120.00	120.00	120.00
02	Hydroxyethyl Cellulose	80.00	90.00	80.00	80.00	80.00
03	Cetostearyl Alcohol	46.70	56.70	46.70	46.70	46.70
04	PVP K30	20.00	-	20.00	20.00	-
05	Ethyl cellulose 10 cps	13.30	13.30	13.30	-	-
06	Ethyl cellulose 50 cps	-	-	-	13.30	33.30
07	Talc	10.70	10.70	10.70	10.70	10.70
08	Magnesium Stearate	10.70	10.70	10.70	10.70	10.70
09	Purified Water	Q.S.	Q.S.	-	-	-
10	Isopropyl Alcohol	-	-	Q.S.	Q.S.	Q.S.
	Avg. Wt. (mg)	301.40	301.40	301.40	301.40	301.40

Table 2: Initial Result - Drug Dissolution and Related Substance

Formulation		*F1*	*F2*
Drug Dissolution			
Time (Hours)		*% Release*	*%Release*
2		35.8	23.1
4		53.7	36.1
8		78.8	61.0
12		85.4	72.0
16		88.7	79.4
20		89.5	87.4
Related Substance			
Impurity	*USP limit*	*F1*	*F2*
Deacetyl impurity Desacetyl-diltiazem	NMT 1.5	0.687	0.130
Total unknown impurity	NMT 0.2	0.328	0.090
Total impurity	NMT 2.0	1.015	0.220

Table 3: Stability Result - Drug Dissolution and Related Substance

Formulation		*F1*	*F2*
Drug Dissolution			
Time (Hrs.)		*%Release*	*%Release*
2		46.1	24.0
4		69.5	39.1
8		87.9	61.3
12		89.8	73.9
16		91.4	82.4
20		93.5	89.4
Related Substance			
Impurity	*USP limit*	*F1*	*F2*
Deacetyl impurity Desacetyl-diltiazem	NMT 1.5	3.662	0.600
Total unknown impurity	NMT 0.2	0.490	0.130
Total impurity	NMT 2.0	4.152	0.730

Formulation Optimization Study

The finalized formulation was optimized using the QbD (Quality by design) approach by varying number of different excipients at a certain level and their impact on the physicochemical properties of the finished drug product.

RESULT AND DISCUSSION

Observed Results

Physical parameter of formulation F1 and F2 was observed to be satisfactory. However, in the formulation F3, 4 and 5, tablet sticking and picking were observed during compression. All trials' initial *in-vitro* drug release profile was observed to be satisfactory and well within the desired specifications (Table 2).

Tablets of formulation F1 and F2 were kept on accelerated stability study conditions and for further evaluation and analysis after packing the tablets in Al strip packs.

On stability, the drug release profile of formulation F1 was observed very high compared to F2. Similarly, impurity level of formulation F1 was observed on a higher level (Table 3), (Figure 2 & 3).

Multiple trials of formulation optimization indicate that formulation F2 is optimum and the selected excipients can be varied up to the defined limit without any change in the properties of the finished product. To concise the article, the results of the trials performed in the formulation optimization are not included here.

DISCUSSION

Diltiazem HCl and its formulations are prone to hydrolysis leading to degradation and an increase in its impurity profile on storage. Numerous pieces of literature indicate that excessive exposure to high moisture content excipients or any manufacturing process involving aqueous medium/system usage can allow moisture update by the blend or solid oral preparation. This moisture uptake can also happen during long-term storage in semi-permeable or permeable containers. The moisture uptake is avoided by taking care in selecting suitable low moisture containing excipients and controlled manufacturing/ processing techniques.

PVP-K30 is primarily used as a binder or viscolyzing agent in controlled release formulation along with release-controlling agents. PVP- K30 is freely wasting soluble and has tendency to act as a capillary forming agent when is present a matrix system. Due to this property may affect the microenvironment by moisture migration within the matrix, allowing close probity of API with available moisture, thus leading to an increased rate of degradation by hydrolysis.

CONCLUSION

Formulation of F 1 contains povidone K-30, which is highly water-soluble and is hygroscopic in nature. It may act as source of extra moisture leading to API's instability and enhanced drug release. Drug release and impurity profile of formulation F2 was observed to be satisfactory at initial and on the stability study conditions. Therefore, this formulation can be considered for scale-up and commercial-scale batch manufacturing.

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