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# STABILITY STUDIES OF THE OPTIMIZED ORAL CONTROLLED RELEASE VERAPAMIL HYDROCHLORIDE TABLET FORMULATIONS

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**ABSTRACT**

In the present study accelerated testing (6 month) and long term testing (12 month) were carried out on Oral Verapamil Hydrochloride control release tablet in order to assess the physical and chemical stability of Verapamil Hydrochloride tablets. All the formulations were tested for disintegration test, % drug content and % drug release over the entire period of testing. These formulations did not show any significant change in any parameter during 12 month and 6 month of testing at 25+5°C/60+5% RH and at 40+2°C/75+5% RH, respectively. All the results were within the acceptable limits. Shelf lives calculated by software *R Gui* were found to be 43.452, 43.577 and 43.234 months at 1, 3 and 6 months for F4 in accelerated stability. However shelf lives were 44.112, 41.634, 41.867 and *42.896 months at 1, 3, 6 and 12 months respectively* in long term stability.

**Keywords:** Accelerated stability testing, Verapamil HCl, Disintegration test, Drug content, Drug release

## INTRODUCTION

The stability and the efficacy of the dosage forms are of the prime importance for the optimum therapeutic outcomes and patient safety[1]. Various physiochemical parameters like presence of additives, compatibility of API with excipients and the environmental and storage conditions has an effect on the stability of a dosage form[2]. Every dosage form has a shelf life during which it remains safe and effective for the patient use. After the shelf life or expiry date, the dosage form lost its effectiveness and may cause some serious health hazards[3]. The excipients used in the formulation, although are inert, can affect the stability of the API thus the shelf life of the formulations. Various pathways of degradation are taken up by the pharmaceutical products like, hydrolysis, oxidation, cyclization and deamination [4].Thus the stability studies have received much importance in developing dosage forms because these studies can monitors the changes in a dosage forms with respect to storage conditions, environmental factors and the type of packing used[5, 6]. Through these studies the shelf life and storage conditions of a particular dosage form are determine that are applicable to all the batches of the same product manufactured and packed with similar fashion. Thus, the stabilities studies should include the testing of those parameters likely to be changed during the storage conditions that can affect the quality, safety and efficacy of the prepared formulations.[6]

Verapamil hydrochloride was discovered in 1962 as an antianginal and antiarythmic and antihypertensive drug. It is also effective as a therapeutic agent for the treatment of cardiomyopathy in children. Chemically it is phenylalkylamine and acts as calcium channel blocker[7]. When given orally 90 % of the drug is absorbed and reaches the maximum plasma concentration within 1-2 hours. However the extensive first pass effect reduces its bioavailability with a very short half life [8]. To maintain the plasma drug levels within the therapeutic window frequent dosing is required. To decrease the dosing frequency and increasing the half life, controlled release matrix

tablets of verapamil hydrochloride were prepared. The present study was conducted to assess the quality and safety of the developed controlled release tablets of verapamil hydrochloride in terms of stability. Accelerated and long term stability studies were carried out by storing the tablets at 30±2° C/40±5 % relative humidity for 12 months and accelerated studies were carried out at 40±2° C/75±5 % relative humidity for 6 months. Different parameters of the tablet dosage form testing will be utilized like disintegration, dissolution, content assay and dissolution (WHO guidelines for stability for stability testing).

## MATERIALS AND METHODS

**Preparation of the formulations:** Different formulations of Verapamil Hydrochloride were prepared by applying central composite design using a software package Design Expert 9 as shown in table 1. These tablets were prepared by compression to form a matrix type controlled release tablet dosage form. Depending upon the response surface methodology the optimization is carried out and F4 formulation was found to be the most optimized formulation.

**Stability studies:** The stability studies were carried out according to the WHO and ICH guidelines. Tablets were taken from each formulation and placed in an amber colored bottle.For accelerated studies the bottles were stored at 40±2° C/ 75±5 % relative humidity. The storage conditions of 25±5° C/65±5% were maintained for 12 months for long term stability studies. For accelerated studies the samples were placed in humidity chamber (NuAir USA). The tablets were tested by taking the samples at an intervals of 0, 3, 6 months for accelerated studies and at intervals of 0,3,6,9 and 12 months for long term stability studies. All the samples were evaluated in term of disintegration, % drug content and % drug release.

**Disintegration test:** Disintegration tests were carried out after the specific intervals by using USP disintegration apparatus. Six tablets were placed in basket rack assembly of apparatus and the basket was moved at the frequency of 29 to 32 cycles per minute at 37±2° C.

**Dissolution studies:** In vitro drug release studies were carried out by using USP dissolution Apparatus II. A phosphate buffer was used as a dissolution medium maintained at 37±2° C. A 5 ml sample was withdrawn after the specific period of time and fresh dissolution medium was replaced to maintain the volume. Then the concentration of the drug in each sample was determined by spectrophotometric analysis after suitable dilutions at wavelength of 230 nm [9].

**Content assay :** The content assay was carried out by developing and validating reverse phase HPLC method by employing reverse phase chromatographic system with the mobile phase of methanol: acetonitrile: water in the ratio of 2: 2:1 v/v/v containing 0.50 mL orthophosphoric acid. The pH was adjusted to 7. C18 3.9×300mm µBondapak (RP) column was used. 1 mL /min was set as the flow rate of the mobile phase. The wavelength 278nm was set for detector. The method was sensitive, precise and linear ($R^2$=0.999) and showed to be excellent in the range of 3.125-37.50 µg/ mL.

**Calculation of Shelf life:** The shelf lives were calculated by RGui software.

## RESULTS

The results of the tests applied for the accelerated stability studies in are presented in table 2. The results showed minor and insignificant changes. The results of long term stability studies are presented in table 3. The results were very much similar to the accelerated stability studies showing the stable formulations. Fig 1 and 2 represents the dissolutions studies performed after the accelerated and long term stability studies and a brand leader Clan SR.

## DISCUSSIONS

The stability of a dosage form means the chemical and physical integrity of the drug product. An ideal drug product must be fully characterized at the start of the study and throughout the shelf life [10]. To characterize the product different parameters were tested as an indicator of stability like disintegration, dissolution and content assay [4]. The developed formulations were tested for short term stability after an interval of 1, 3 and 6 months at the accelerated condition of 40±2° C and 75±5 % RH. For the long term stability studies the formulations were stored at 25±5° C and 65±5 % RH and tested after a time period of 1,3,6,9 and 12 months. There were little changes in the results over the period of time. The changes in the values of parameters were tested by Analysis of Variance (ANOVA) and found insignificant. The results have proved that all the formulations are stable and capable of storage over a longer period of time. The results of accelerated stability studies are presented in table 2.The disintegration time of all the formulations at 40±2° C

and 75±5 % RH after one month ranged from 24±0.94 min of formulation F5 to 64±0.34 min. The disintegration time after 3 and 6 months was in range of 24±23 to 63±12 min and 23±13 to 61±13 respectively. These results showed an insignificant change in the disintegration time showing the stability of the polymers used in formulations and physical integrity of the product [11]. The disintegration time of the optimized formulations F4 were 63±0.12, 62±.07 and 59±0.10 after one, two and three months respectively making it the most stable formulation. The results of dissolution tests for the short term testing also indicated a stable formulation. The % dissolution of all the formulations ranged from 92±.78 to 102±0.08 after one month. The value of % dissolution of the formulations after 3 and 6 months ranged from 91±0.58 to 100±0.11 and 96±78 to 100±0.16 after 3 and 6 months respectively. In case of the formulation F4, the optimized one the, % dissolution values were 102±0.11, 101±0.05 and 101± 0.13 after one, two and three months respectively. These insignificant changes in the dissolution value indicated the same release behavior of the drug and same functioning and release retarding effect of polymer. Thus the prepared formulations are stable in terms of dissolution[12]. The assay of the active pharmaceutical ingredient is included in the stability testing by the ICH guidelines. It indicates the stability and compatibility of the active ingredient with the excipients over the longer periods of time. The % contents of all formulations range from 95.76±0.23 of formulation F3 to 99.98±0.042 after a period of one month. Similarly the values of content assay of the formulations vary from 93.88±0.43 to 99.99±0.022 after 3 months and from 93.82±0.40 to 99.99±0.13 after 6 months. These results are within pharmacopoeia limits indicating the stability of API and the product. The shelf life of the product the most desired characteristic is then calculated based on the results after the testing at specific intervals. The shelf life of the formulations varied from 3.419 to 43.452. The optimized formulations have the highest value of shelf life. The formulation F4 has a shelf life of 43.452. The value of shelf life of the optimized formulation after 3 months was 43.577 while after 6 months this value of shelf life was 43.23, making it the most stable formulation. The results indicated minor and statistically insignificant changes, as revealed by ANOVA, in the shelf life of all formulations over the period of six months at elevated temperature and humidity conditions showing the stable control release formulations of Verapamil Hydrochloride. Similar results were obtained in another study reported by Farya et al., [13] .

The results of long term stability studies also confirmed the physical and chemical stability of formulations. Like accelerated studies, the results in long term studies were obtained with minor changes. In case of disintegration the value of optimized formulation F4 changes from 63±0.12 to 60±0.01 during the course of 12 months and in case of dissolution the value range from 102±0.11 to 100±.03. The % age contents varied from 99.98±0.042 to 99.67±.011 and a shelf life varied from 44.112 to 42.896. These minor changes in the results of all the tested parameters were insignificant indicating a stability of the polymers used and the verapamil hydrochloride and a stable dosage form. The drug release studies of all the formulations after accelerated and long term studies and a brand leader Clan SR were carried out. No significant changes were observed in the drug release profiles after short and long term stability studies. This result were consistent with a study on Verapamil Hydrochloride matri tablets by Dimitrov et al.,[14]. The drug release profile of the optimized formulation F4 was identical to that of Clan SR in terms of % release of drug with respect of time.

## CONCLUSIONS

The accelerated stability studies was performed following ICH guidelines and the shelf life was calculated by software *R Gui, was* found to be unchanged during the entire period. Moreover the results of the present study also indicated that the formulations remained chemically and physically stable during the accelerated stability and long term stability. The formulation F-4 was found to be the most stable formulation among all the trial formulation both in shelf life and other physicochemical characteristics.

**Table 1. Different Formulations of Verapamil HCl tablets having weight 750 mg/ tab.**

| Formulations | Verapamil HCL(mg) | HPMC (mg) | Na. CMC(mg) | Acacia (mg) | Xanthan gum (mg) | Mg. Stearate (mg) | Aerosil (mg) | Titanium Dioxide (mg) | Avicel PH 101 |
|---|---|---|---|---|---|---|---|---|---|
| F 1 | 240 | 285 | - | - | - | 5 | 5 | 15 | 200 |
| F 2 | 240 | 214 | 71 | - | - | 5 | 5 | 15 | 200 |
| F 3 | 240 | 160 | 125 | - | - | 5 | 5 | 15 | 200 |
| F 4 | 240 | 125 | 160 | - | - | 5 | 5 | 15 | 200 |
| F 5 | 240 | - | - | | 285 | 5 | 5 | 15 | 200 |
| F 6 | 240 | - | - | 214 | 71 | 5 | 5 | 15 | 200 |
| F 7 | 240 | - | - | 160 | 125 | 5 | 5 | 15 | 200 |
| F 8 | 240 | - | - | 125 | 160 | 5 | 5 | 15 | 200 |

**Table. 2: Stability Data of Optimized Oral Controlled Release Verapamil Hydrochloride at 40±2Ċ and 75±5% RH**

| Parameter | Unit | Period | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|---|---|
| Disintegration Test (n=6) | Min | 1month | 28±0.91 | 60±0.56 | 55±0.75 | 64±0.34 | 25±0.94 | 45±0.25 | 40±0.78 | 42±0.36 |
| Dissolution Test (n=6) | % | | 99±0.32 | 98±0.51 | 99±0.11 | 102±0.08 | 97±0.61 | 92±0.78 | 95±0.18 | 101±0.99 |
| Content Assay (n=6) | % | | 99.08±0.35 | 97.88±0.51 | 95.76±0.23 | 99.98±0.04 | 99.99±0.012 | 98.68±0.03 | 97.28±0.72 | 96.93±0.54 |
| Shelf Life (n=6) | (months/weeks) | | 40.612 | 39.572 | 40.045 | 43.452 | 41.113 | 38.419 | 40.444 | 38.989 |
| Disintegration Test (n=6) | Min | 3month | 28±0.88 | 59±0.76 | 56±0.75 | 63±0.12 | 24±0.23 | 44±0.28 | 40±0.67 | 41±0.86 |
| Dissolution Test (n=6) | % | | 93±0.42 | 97±0.19 | 97±0.61 | 100±0.11 | 94±0.88 | 91±0.58 | 96±0.59 | 99±0.50 |
| Content Assay (n=6) | % | | 98.08±0.52 | 98.78±0.72 | 93.88±0.45 | 99.99±0.02 | 99.45±0.562 | 97.22±0.21 | 97.46±0.41 | 97.78±0.57 |
| Shelf Life (n=6) | (months/weeks) | | 40.612 | 39.572 | 40.045 | 43.577 | 41.144 | 37.734 | 38.786 | 37.234 |
| Disintegration Test (n=6) | Min | 6month | 27±0.97 | 58±0.83 | 56±0.88 | 61±0.13 | 23±0.44 | 42±0.88 | 38±0.79 | 41±0.89 |
| Dissolution Test (n=6) | % | | 95±0.33 | 97±0.37 | 95±0.72 | 100±0.16 | 92±0.78 | 97±0.98 | 96±0.78 | 97±0.77 |
| Content Assay (n=6) | % | | 96.23±0.42 | 97.72±0.82 | 93.82±0.40 | 99.99±0.01 | 99.67±0.876 | 96.34±0.54 | 96.78±0.56 | 97.21±0.67 |
| Shelf Life (n=6) | (months/weeks) | | 39.672 | 38.654 | 40.045 | 43.234 | 39.367 | 38.756 | 38.756 | 37.222 |

**Table. 3: Stability Data of Optimized Oral Controlled Release Verapamil Hydrochloride at 25+5°C/60+5% RH**

| Parameters | Unit | Period | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|---|---|
| Disintegration Test (n=6) | Min | 1month | 27±0.71 | 60±0.56 | 53±0.89 | 63±0.12 | 24±0.45 | 43±0.63 | 40±0.99 | 41±0.30 |
| Dissolution Test (n=6) | % | | 93±0.47 | 98±0.91 | 96±0.75 | 102±0.11 | 95±0.76 | 90±0.89 | 95±0.18 | 100±0.09 |
| Content Assay (n=6) | % | | 96.11±0.85 | 95.48±0.66 | 95.09±0.63 | 101.98±0.042 | 97.99±0.55 | 98.08±0.51 | 96.45±0.23 | 95.04±0.67 |
| Shelf Life (n=6) | (months/weeks) | | 38.535 | 38.598 | 41.123 | 44.112 | 40.324 | 38.321 | 39.672 | 36.498 |
| Disintegration Test (n=6) | Min | 3month | 26±0.75 | 55±0.95 | 53±0.98 | 62±0.07 | 22±0.63 | 43±0.78 | 40±0.99 | 40±0.44 |
| Dissolution Test (n=6) | % | | 91±0.32 | 95±0.45 | 97±0.64 | 101±0.05 | 94±0.23 | 88±0.61 | 90±0.29 | 99±0.50 |
| Content Assay (n=6) | % | | 98.08±0.52 | 98.78±0.72 | 93.88±0.45 | 99.69±0.02 | 95.49±0.73 | 96.72±0.59 | 94.71±0.82 | 95.48±0.88 |
| Shelf Life (n=6) | (months/weeks) | | 38.678 | 38.667 | 38.278 | 41.634 | 40.234 | 36.956 | 36.523 | 35.645 |
| Disintegration Test (n=6) | Min | 6month | 26±0.34 | 55±0.31 | 54±0.908 | 59±0.10 | 21±0.51 | 40±0.88 | 37±0.65 | 39±0.67 |
| Dissolution Test (n=6) | % | | 93±0.41 | 95±0.20 | 93±0.65 | 101±0.13 | 90±0.60 | 98±0.67 | 95±0.70 | 95±0.90 |
| Content Assay (n=6) | % | | 94.56±0.34 | 96.92±0.61 | 93.59±0.36 | 99.99±0.013 | 99.99±0.14 | 93.19±0.82 | 93.71±0.55 | 96.18±0.52 |
| Shelf Life (n=6) | (months/weeks) | | 37.700 | 36.245 | 36.234 | 41.867 | 36.354 | 36.276 | 35.407 | 34.210 |
| Disintegration Test (n=6) | Min | 12month | 25±0.77 | 56±0.52 | 53±0.69 | 60±0.01 | 20±0.74 | 38±0.79 | 37±0.60 | 40±0.51 |
| Dissolution Test (n=6) | % | | 94±0.63 | 92±0.99 | 93±0.37 | 100±0.03 | 93±0.59 | 97±0.77 | 96±0.29 | 95±0.35 |
| Content Assay (n=6) | % | | 94.20±0.80 | 95.50±0.77 | 91.66±0.33 | 99.67±0.011 | 95.47±0.78 | 94.60±0.50 | 94.87±0.47 | 93.71±0.54 |
| Shelf Life (n=6) | (months/weeks) | | 37.034 | 37.611 | 38.0212 | 42.896 | 36.456 | 36.700 | 37.223 | 35.557 |

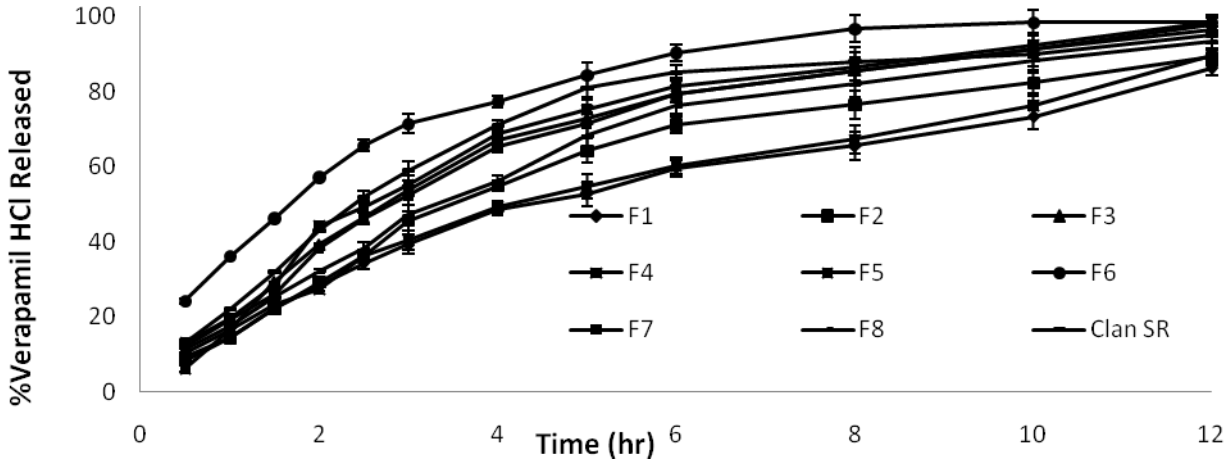


**Fig. 1: Dissolution Profile (Mean±SD) of the Optimized Formulation of Verapamil Hydrochloride and Calan SR® tablets After Conducting Accelerated Stability**

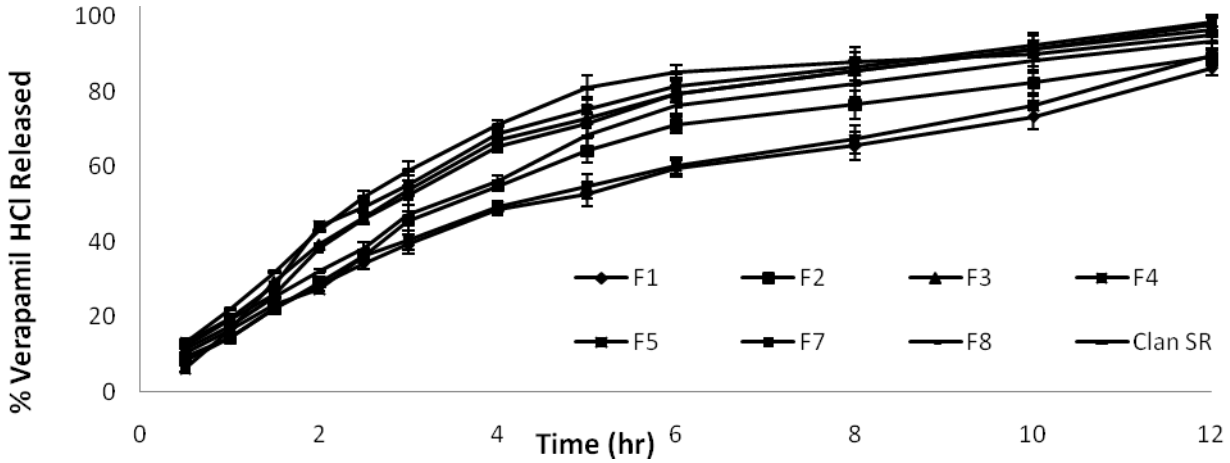


**Fig. 2): Dissolution Profile (Mean±SD) of the Optimized Formulation of Verapamil Hydrochloride and Calan SR® tablets After Conducting long term Stability**

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