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Research Article

# ASSESSMENT OF THE IMPACT OF FORMULATION AND PACKAGING ON THE STABILITY OF CABERGOLINE TABLETS

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**ABSTRACT**

The aim of this study was to investigate the impact of excipients, film coating and packaging materials on the stability of Cabergoline tablets. Direct compression was selected and Cabergoline tablet formula designed after the properties of excipients had been well studied to be convenient for such low soluble unstable drug in humidity, and using differential scanning calometry (DSC) as a rapid tool to assess the compatibility between them at preformulation level.

The amino acid L-leucine was used in the formula as a stabilizer to improve the chemical stability of the drug, and the effect of a film coating was investigated. These formulas were manufactured, and entered into cabinets for accelerated and long term stability, after they were packaged in two different materials of aluminum, polyvinilidyn chloride (pvdc) which protect from humidity, and without any desiccant material.

The results affirmed that the use of non- hygroscopic excipients, film coating and Aluminum as packaging materials were of great importance for the preservation of Cabergoline tablets during accelerated and long term studies.

**Keywords:** DSC, Humidity, Stability, Film coating, Aluminum

## INTRODUCTION

Cabergoline has emerged as a first-line in the treatment of prolactinomass disorders and Parkinson's disease at early stages because it is dopamine D2 receptor agonist[1], less severe side effects, and more convenient dosing schedule than the older bromocriptine.

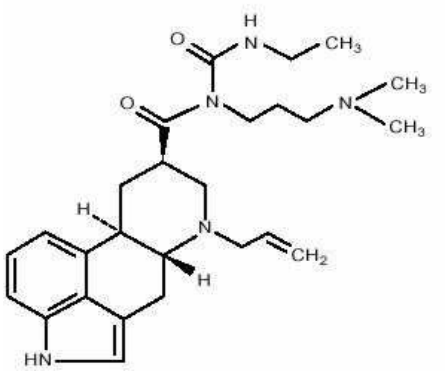

**Fig. 1: Shows Chemical structure of Cabergoline**

Since, Cabergoline has poor chemical stability as it is very sensitive to light and moisture because of its chemical structure, Cabergoline has amid group Fig1, which is susceptible to hydrolysis[2] and its low dose increase its degradation as it is in more contact with the excipients in the tablet[3].

It also shows polymorphism since it has two forms(I, V)[4].

All of these reasons make reaching a successful and stable drug product difficult, critical and effective cost process.

The product is commercially available today as an uncoated tablets packaged in amber glass containing desiccant in it, under the brand name Dostinex® (Pfizer).

This type of packaging is expensive and so bulky that it causes many difficulties during transport, shipping and storage.

Direct compression is well known process for tablets production. It has many advantages over the wet granulation process including the most important being fewer processing stages and the elimination of heat and moisture effects[5].

The aim of this paper is to investigate the effects of excipients, film coating and packaging type on the accelerated and long term stability of Cabergoline as tablets dosage form.

The work covered preformulation and formulation study to select the suitable excpients compatible with the active ingredient, and may increase its long term stability. Differential scanning calometry was used as versatile technique for the preformulation study.

The selection criteria for excipients was having low hygroscopic tendency depending on equilibrium moisture content (EMC)[6]. Amino acid L-Leucine was used as a stabilizer[7].The tablets were prepared by direct compression and film coated (HPMC) to increase the protection of Cabergoline against moisture transport[8].

Finally, the effect of the package type was carefully studied through aluminum and polyvinilidyn chloride (pvdc) which are good barrier to the water vapor[9].

## MATERIALS AND METHODS

### Materials

Cabergoline form I was supplied by chemswiss, L-leucine was from China/Karince, HPMC was obtained from China\shandong Head, PEG4000 was from Russia\hopkem, and Titanium dioxide was from Czech\precheza.

Methylene chloride was purchased from UK\Ineos, Ethanol100% was from EU\solvochem.Lactose anhydrous DC was supplied by Germany\DMY,

Croscarmillose sodium, Avicell pH 112 (MCC), Aerosil and Magnesium stearate were purchased from Germany\JRS.

Acetonetril, methanol were from sigma\Germany, Phosphoric acid was obtained from scharlau\Euro, Triethylamin was from scp\England, Dihydrogen potassium phosphate was from avonchem\U.K, and Hcl 37% was from merk\ Germany.

### Preformulation

### Excipients compatibility study by Differential Scanning calometery

DSC Linseis – l63- PT10 was used to study samples weighing 5mg of drug alone, excipient alone and binary mixtures of drug: excipient at 1:1 ratio in alumina pans at different conditions:

1-after direct mixing, 2- after 14 days in closed bottle (at ambient), 3- after 14 days in closed bottle (at 40°C), 4- after 14 days in opened bottle (at long term condition)[10], at heating rate 10C°/min in the range between 25-300 C°, each sample was replicated.

**Manufacturing, coating and packaging**

Direct compression was used, the equipment was 1991- Cadmach, CmD3 B16, rotary tablet press, d-type (25 mm), punches were rounded and of 6 mm diameter. To ensure good homogeneity for the little active ingredient the blending was performed in a plastic bag for 3-5 minutes, then passing it through 0.4 mm sieve.

Two formulas were coated until reaching 7% of the tablet weight with coating solution (Titanium dioxide 0.4%, Hypromellose 2910 (40-60) cp 2.1%, PEG 4000 0.4%, HPMC 606(6) cp 4.9%, Ethanol 99% 70%, methylene chloride 61.6%). These percentages are of the total batch coated and these polymers were selected because of their hydrophilic properties that are desirable for the limited solubility of the drug. In addition, they were well known and used in the coating of similar moisture sensitive drugs such as amoxicillin. the equipment was (BG-E) depending on coating by drizzle (20 rpm, product temperature is 40 C°, inlet air temperature is 48 C°, air pressure is 2.5 bar).

The formulas A, C packaged with cold form Aluminum, formula B was divided in two parts: the first one packaged with aluminum, and the other packaged with (pvdc).

**In- process quality control**

**In-process manufacturing**

Weight uniformity test by weighing 20 tablets individually and calculating the average. Friability test calculated the loosed portion of the weight of the tablets after rotating by Erwicka (Dr.schleuniger pharmaton\Germany) for 4 minutes. Hardness test used the average of 6 tested tablets by Erwicka (Dr.schleuniger pharmaton \Germany). Disintegration by placing one tablet in each of the six tubes of the basket apparatus (Dr.schleuniger pharmaton \Germany) using water as a medium, maintained 37C°±2, after 15 minutes lifted the basket from the water and observed the tablets.

**In-process coating**

Weight uniformity test, disintegration test as above.

**Uniformity of dosage units**

This test was performed before the coating according to USP 34 by assaying 10 tablets individually and calculating the acceptance value (AV).

**Accelerated and long term stability studies**

Specifications which were expected to be affected by stability conditions were studied at accelerated conditions (40C°, 75% RH) at 0, 1, 3, 6 months. Also they were studied at longer term conditions (30C°, 65%. RH) at 0, 3, 6, 9, 12 months, cabinets were Binder\Germany\08-54156.

**Physical tests**

Friability test was performed for the uncoated formula A, hardness test for the uncoated formula A, and the coated formulas B, C.

**Chemical tests**

**Karl Fischer**

The total moisture content was identified by assaying the water content of approximately 120 mg by fisher reagent and methanol.

**Assay**

According to USP 34 this test was performed, HPLC (LC 20 AT SPD 20 A Shimadzu) and column (Kromasil Akzonobel Sweden) was used. Mobile phase was a mixture of buffer of PH=2 and acetonitrile 84:16, flow rate was 1.3, injection volume was 20 µl.

**Dissolution**

USP II Dissolution apparatus (coply, U.K) was used, and according to USP 34, 50 rpm, medium :0.1 Hcl 500 ml, test duration was 15 minutes for uncoated formula A and 20 minutes for coated formulas B, C.

**Impurity limits**

According to USP 34 impurity A1(which is chemically R-quinoline-carboxylic acid) was recognized depending on RRT=0.8 (relative retention time), after comparing by the same assay method between resolution solution (resulted from drug degradation with NaoH and Hcl) and test solution (assay preparation), and the limits of impurity A1 were identified by calculating the percentage of the impurity A1, and unspecified impurities relatively to the main peak of the drug(which is chemically ergoline-8β-carboxamide, RRT=1.0) and that certified how the drug hydrolyzed.

**Verification of The Assay**

The key parameter is specificity, placebo was compared with the sample of any formula in the assay test and Resolution factor with the nearest peak was identified. Peak purity of each ingredient was detected by HPLC-PDA (photo diode array) (USP 34 NF29 (2626)), system suitability was verified by calculating RSD of triplicates and finding out of the number of theoretical plates.

**RESULTS AND DISSCUSSION**

**Physicochemical properties of Cabergoline and excipients choice**

Cabergoline is a white crystalline powder soluble in ethyl alcohol, chloroform, and N, N-dimethylformamide (DMF); slightly soluble in 0.1N hydrochloric acid; very slightly soluble in n-hexane; and insoluble in water. It has form I with melting range (100-110 C°), form V with melting range(60-65 C°), so the first one was more preferable and used for its expected stability. Because of its sensitivity to moisture, the excipients of direct compression were selected that have good solubility in water and low value of EMC especially the diluent Lactose anhydrous (EMC: at 25C°, RH 43%: 0.2%), Avicell PH 112 as a dilluent-binder (EMC: < 1.5%), Coroscarmillos sodium as a disintegrant, colloidal silicone dioxide as a glidant, magnesium stearate as a lubricant, which was already mentioned in[6], L-leucine as a stabilizer which is in accordance to[7].

**DSC Results**

Fig. 2: Shows

Caber 1: drug alone

Caber 2: drug with excipient in closed bottle.

Caber 3: drug with excipient for 14 days in closed bottle.

Caber 4: drug with excipient for 14 days at 40C° in closed bottle.

Caber 5: drug with excipient for 14 days at long term in opened bottle.

Caber 6: drug with excipient for 4 weeks at accelerated in opened bottle. (in some cases).

**Drug with lactose mixtures**

DSC curve of Cabergoline form I exhibit endothermic peak with melting range between 100-110C° in agreement with literature values[4].

In this mixture Tpeak of the drug did not exhibit any remarkable change at all conditions. Tpeak for lactose anhydrous was at 247C°, and with caber 6 two endothermic peak were seen, one of them at 159.2C° related to dehydration and the other is due to melting point of lactose. It looked like the lactose did bind to the water and converted to monohydrate lactose, but this excipient has chemical stability similar to that of the anhydrous lactose, and this is previously reported[11].

**Drug with MCC (Avicel 112) mixtures**

Tpeak of the drug didn't change at all conditions (Fig 2, b). Avicel exhibited wide endothermic peak at 86 C° attributed to water loss, since it absorbed the water because of its mechanism as binder-

disintegrant, also it exhibited small endothermic peak at 190C° becomes greater at all conditions attributed to rupture of the cellulose glecosidic bonds and this is previously mentioned[12].

**Drug with croscarmellose sodium mixtures**

Tpeak of the drug didn't change at all conditions (Fig 2, c). Croscarmellose exhibited wide peak at low temperature 130 C° attributed to water loss. Because of its mechanism as it is disintegrant, it absorbs water but it is still stable[13], and as it resembles MCC in its structure it has the same second peak for the same reason.

**Drug with Aerosil mixtures**

Tpeak of the drug didn't change at all conditions (Fig 2, d). Aerosil does not have any peak because it is amorphous powder.

**Drug with MS mixtures**

Tpeak of the drug didn't change at all conditions (Fig 2, e) and MS exhibited endothermic peak at melting point 140.6C° and another peak at 289C° attributed to Mg palmitate as an impurity or of high-melting polymorphism and this reported previously[14].

**Drug with L-Leucine mixtures**

T peak of the drug didn't change at all conditions (Fig 2, f). L-Leucine showed melting and decomposition endothermic peak at 300C° and by mixing it with the drug it changed to lower value because of its decreased purity, and this is consistent to previous finding[15].

Since our aim is simply determining the level of interaction of the drug with different excipients, all of the excipients above were compatible with Cabergoline at all conditions and this is consistent with previous conclusions[14].

**Formulation Results**

Three formulas were prepared. A and B had l-leucine as a astabilizer A was uncoated B was film coated and C did not have l- leucine and was film coated.

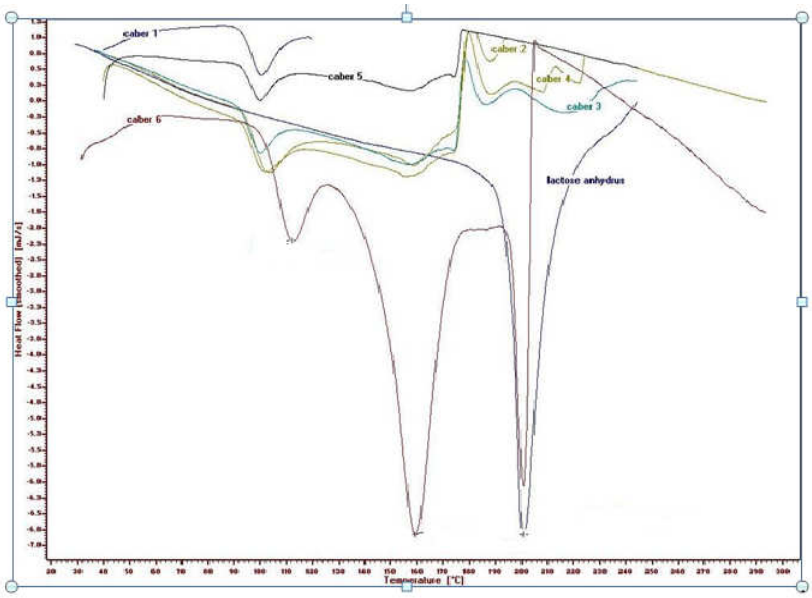


**Fig. 2.a: Shows drug with lactose mixtures**

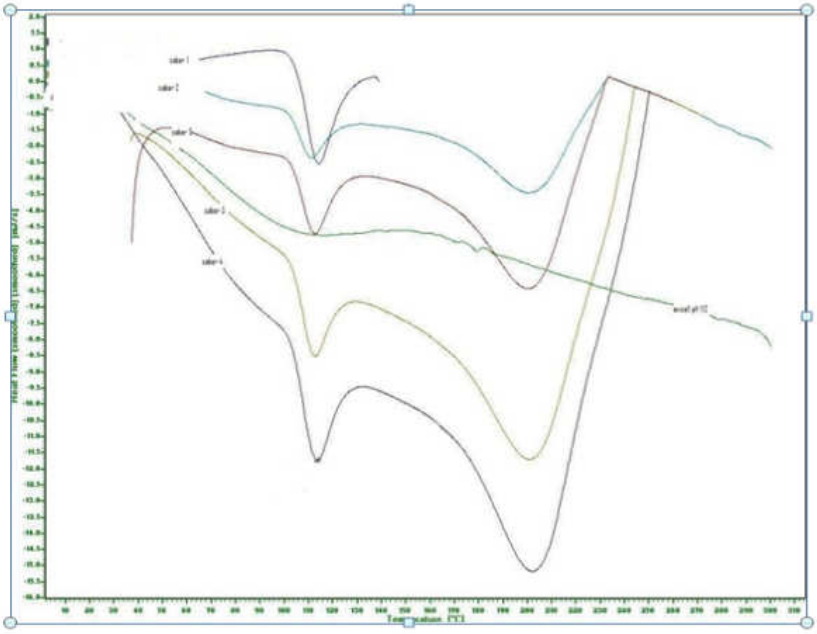

**Fig. 2.b: Shows drug with MCC (Avicel 112) mixtures**

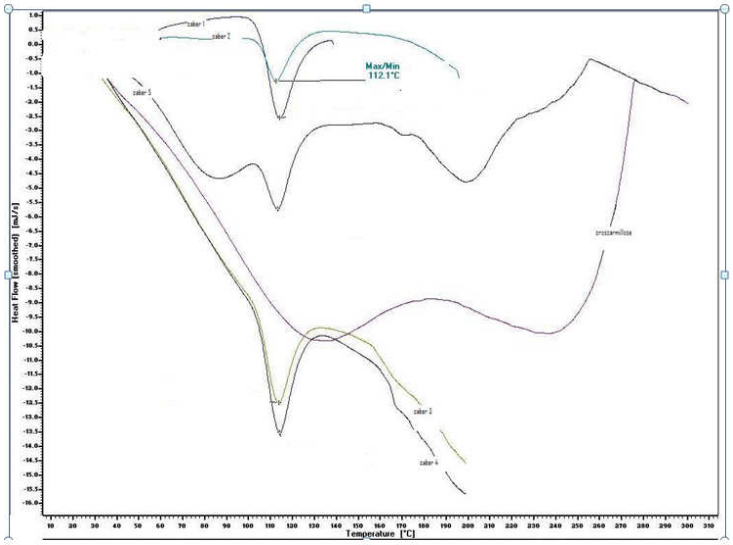


**Fig. 2.c: Shows drug with croscarmellose sodium mixtures**

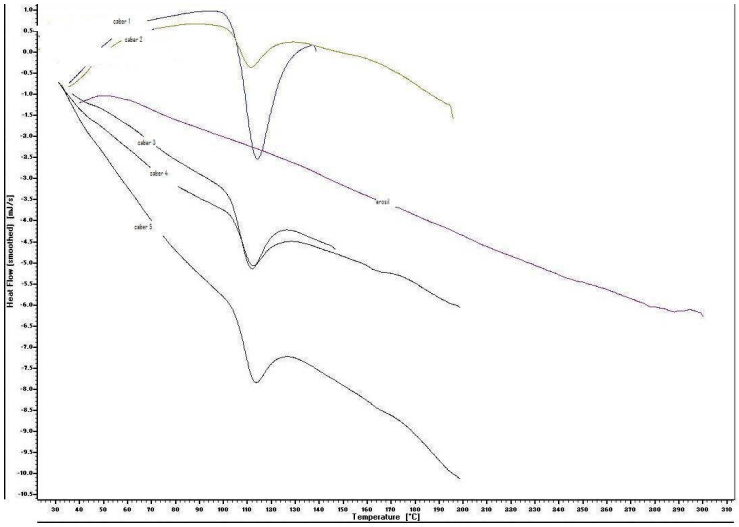


**Fig. 2.d: Shows drug with Aerosil mixtures**

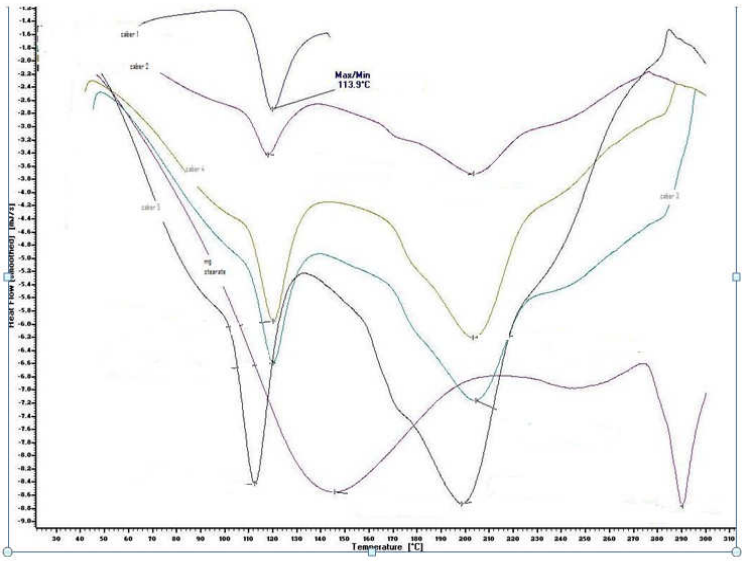


**Fig. 2.e: Shows drug with MS mixtures**

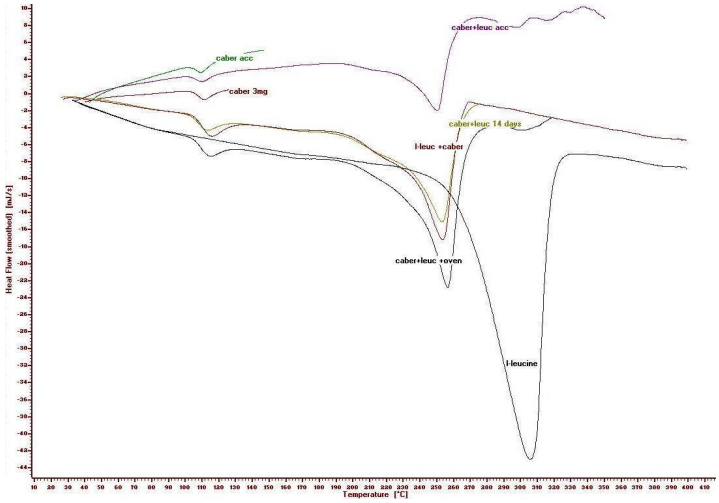


**Fig. 2.f: Shows drug with L-Leucine mixtures**

**Table 1: Shows A, B had l-leucine as a stabilizer, A was uncoated, B was film coated, C had not l- leucine and film coated.**

| **A uncoated tablet** | **%** |
|---|---|
| Cabergoline | 0.63 |
| Lactose Anhydrous | 61.87 |
| MCC 112 | 21.75 |
| Croscarmellose Na | 10 |
| Aerosil | 0.75 |
| Mg stearate | 0.5 |
| L-Leucine | 4.5 |

| **B Coated tablet** | **%** |
|---|---|
| Cabergoline | 0.63 |
| Lactose Anhydrous | 61.87 |
| MCC 112 | 21.75 |
| Croscarmellose Na | 10 |
| Aerosil | 0.75 |
| Mg stearate | 0.5 |
| L-Leucine | 4.5 |

| **C Coated tablet** | **%** |
|---|---|
| Cabergoline | 0.63 |
| Lactose Anhydrous | 64.125 |
| MCC 112 | 23.5 |
| Croscarmillose Na | 10 |
| Aerosil | 0.75 |
| Mg stearate | 1 |

**In-Process Quality Control Tests Results**

**In-manufacturing process**

The tablets were circular (6 mm diameter, 2.5 mm thickness), and of acceptable weight uniformity in both formulas because none of the tablets had weights differed with more than the double of 10 % of average weight (since tablet weight is below 130 mg), and the weights of tow tablets did not exceed that percentage (USP). Each of the six tablets in each formula disintegrated in the specific time.

**In-coating process**

The tablets after coating also were of acceptable weight uniformity in both formulas because none of the tablets had weights that exceeded the 10 % of average weight (USP), which also achieved of the desirable percentage of coating thickness. Each of the six tablets in each formula disintegrated in the specific time.

**Uniformity of Dosage Units Results**

For the formula which did not contain L-Leucine the test was passed because the acceptance value AV < L1: L1 = 15, AV = $|M- \bar{X}| + Ks$

$\%98.5 < \bar{X} < 101.5 \Rightarrow M = \bar{X} = 101.34 \Rightarrow AV = Ks = 2.4 \times 1.29 \Rightarrow AV \approx 3.096$.

For the other formulas that did have L-Leucine, the test was also passed, since $\bar{X} = 101.98 > 101.5 \Rightarrow$

$M = 101.5 \Rightarrow AV = | 101.5 - 101.98 | + 2.4 \times 1.23 \Rightarrow AV = 3.43 < L1$.

**Accelerated Stability Results**

**Physical tests results**

After 6 months the hardness of formula A decreased more than the formulas B, C. The film coating provided the tablets with more hardness with time. Which meant that it acted as a barrier against humidity absorption (the cause of hardness decreasing), which is similar to that discussed in[16]. The uncoated tablets absorbed 4.5% of humidity whereas the coated ones absorbed 2.5 % only. Friability for formula A was not be affected by the decrease in hardness and was still within the specification limit at all times. Also after 1 month the hardness of formula B pvdc decreased more than the formula BAL.

So the effect of packaging was clear, therefore the use of coating and aluminum was beneficial.

**Table 2: Shows in-manufacturing process tests results**

| Average weight of 20 tablets (mg) | | Hardness (N) Average of 6 tablets ±SD | | Disintegration time (min) | |
|---|---|---|---|---|---|
| With leucine | Without leucine | With leucine | Without leucine | With leucine | Without leucine |
| 80 | 81.3 | 64 ±5 | 67.33±4 | 2 | 1.3 |

**Table 3: Shows in-coating process tests results**

| Average Weight of 20 tablets (mg) | | Disintegration time (min) | |
|---|---|---|---|
| With leucine | Without leucine | With leucine | Without leucine |
| 85.5 | 88 | 5 | 4 |

**Table 4: Shows Physical tests results of accelerated stability**

| | Friability | Hardness (N) ±SD | Formula |
|---|---|---|---|
| At zero point | %1 > % 0.01 | 64±5 | A |
| | - | 111±7 | B |
| | - | 130±6 | C |
| After | %1 > % 0.4 | 44±4 | A |
| one month | - | 125±8 | BAL |
| | - | 67±3.4 | B pvdc |
| | - | 121 ±5.5 | C |
| After | %1 > % 0.08 | 49±3 | A |
| 3 months | - | 129±9 | B AL |
| | - | 122±6 | C |
| After | %1 > % 0.08 | 47±2.4 | A |
| 6 months | - | 108±4.5 | B AL |
| | - | 125±5 | C |

**Table 5: Shows chemical tests results of accelerated stability**

| | Dissolution % ±SD | Impurity limit | | % Assay | % M.C | Formula |
|---|---|---|---|---|---|---|
| | | unspecified impurity NMT%0.5 | A1 NMT 2% | | | |
| At zero | 88.3±5 | --- | --- | 98 | 1.76 | A |
| point | 84±3 | --- | --- | 96 | 1.76 | B |
| | 85±4.2 | --- | --- | 98 | 1.85 | C |
| After one | 86.2±3.5 | --- | 2%> | 98 | 1.95 | A |
| month | 84.5±2.4 | --- | 2%> | 96 | 1.89 | BAL |
| | --- | --- | 16% | 70 | 3.14 | Bpvdc |
| | 87±5.6 | --- | 2%> | 96 | 1.93 | C |
| after | 85.5±3 | 0.5> | 2%> | 92 | 1.94 | A |
| 3 months | 95.79±5 | 0.5> | 2%> | 90 | 1.99 | B |
| | 90.6±4.4 | 0.5> | 2%> | 90 | 2.05 | C |
| after | 84.2±2 | 0.5> | 3.5% | 90.4 | 1.70 | A |
| 6 months | 86.2±4 | 0.5> | 2% | 91.5 | 1.77 | B |
| | 86.9±3.1 | 0.5> | 2%> | 89 | 1.86 | C |

**Chemical tests results**

The formulas had similar M.C% over all the points except for formula B pvdc.

That meant that the pvdc package was less protective of moisture than aluminum one, and this is consistent with that mentioned in[17] that the moisture vapor transit rate(m v t r) at(38C°, 90% RH)for aluminum, pvdc are 0.0001, 0.3-0.75 g\m²\day respectively.

With regard to assay, the formulas had similar results over the all points and passed in the accepted range 90-110% (fig 3 a, b).

This is in agreement with what previously was said in[9] that after six months of accelerated stability the assay of drug packaged in aluminum was 100%.

The formula B pvdc, failed after one month because it was 70% < 90-110% (fig 3, c), that showed the strong correlation between the moisture content and drug degradation.

All the formulas at zero point did not exhibibit any impurity (fig 3, a), and after one month formula B pvdc showed impurity A1= 16% > 2% (fig 3, c). So the effect of packaging type is important for formula protection against moisture which caused drug degradation. At the end of the sixth month the impurities were in formula C (< 2%), B (2%), A (3.5%) respectively (fig 3, b), so the film coating in formulas B(with L-leucine) and C (without L-leucine) was more effective in protecting from degradation than L-leucine alone in formula A.

The dissolution % of all formulas were not less than Q+5%:75+5% so the film coating didn't affect on the release rate of the drug.

**Long Term Stbility Results**

**Physical tests results**

Results were consistent with the results from the accelerated tests, after discarding the formula B pvdc because of its unaccepted specifications. (Table 6)

**Chemical tests results**

Results had less severe changes than the results from the accelerated tests especially in assay and impurities limits tests. Some small changes in the assay results may be attributed to analytical errors, and after all stability studies which were performed as per ICH guidelines, the optimized formulations A, B, C showed no significant variations for the tablets parameters and they were stable for the specified time period[18].

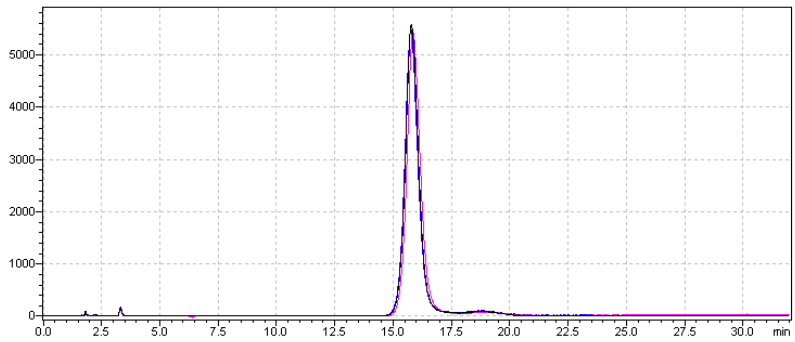


**Fig. 3.a: Shows at zero point, assay of A, B, C**

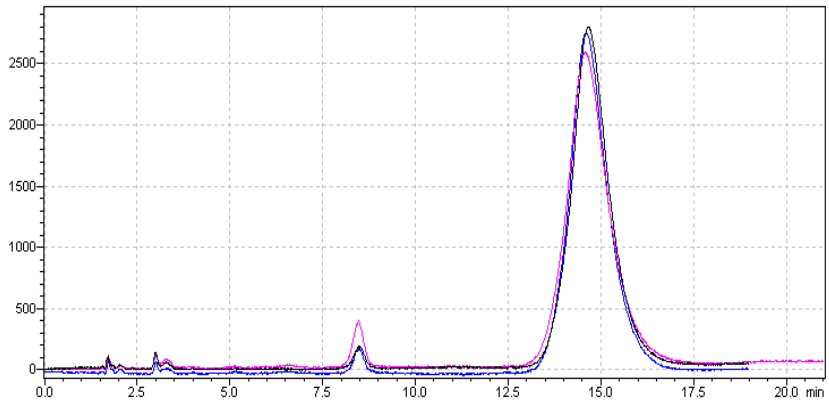


**Fig. 3.b: Shows after 6 months, assay of A(pink), BAL(blue), C(black)**

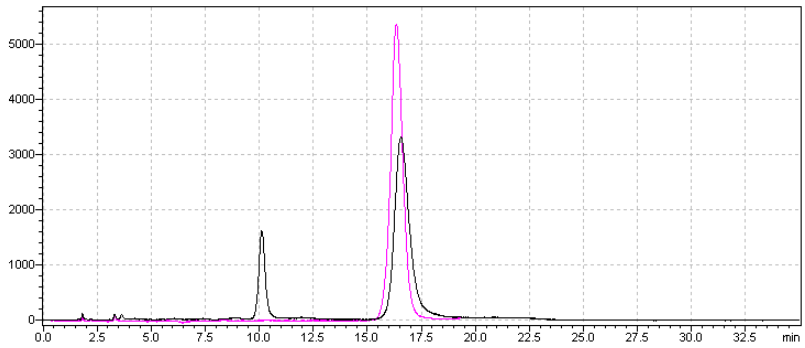


**Fig. 3.c: Shows after one month, assay of BAL(pink), BPvdc(black)**

**Table 6: Shows Physical tests results of long term stability**

| | **Friability** | **Hardness (N)±SD** | **Formula** |
|---|---|---|---|
| At zero point | %1 > % 0.01 | 64±5 | A |
| | - | 111±7 | B |
| | - | 130±6 | C |
| After | %1 > % 0 | 49±4 | A |
| 3 months | - | 126±6 | B |
| | - | 115±7.4 | C |
| After | %1 > % 0.08 | 53±2.5 | A |
| 6 months | - | 127±7.3 | B |
| | - | 122±8.9 | C |
| After | - | 47±3.2 | A |
| 9 months | - | 119±7 | B |
| | - | 119±5 | C |
| After 1 Year | %1 > %0.0 50±4 A | | |
| | - 120±5.5 B | | |
| | - 130±8 C | | |

**Table 7: Shows chemical tests results of long term stability**

| | Dissolution | Impurity limit | | %Assay | % M.C | Formula |
|---|---|---|---|---|---|---|
| | % ±SD | Unspecified | A 1 | | | |
| At zero | 88.3±5.1 | - | - | 98 | 1.76 | A |
| point | 84±3 | - | - | 96 | 1.76 | B |
| | 85±4.2 | - | - | 98 | 1.84 | C |
| After | 94.45±6.1 | - | %2> | 98 | 1.84 | A |
| 3 months | 90±4.1 | - | %2> | 96 | 1.70 | B |
| | 91±5.3 | - | %2> | 96 | 1.83 | C |
| after | 87.8±2.4 | %0.5> | %2> | 97.6 | 2.02 | A |
| 6 months | 86.4±3 | %0.5> | %2> | 96.1 | 1.56 | B |
| | 88.4±4 | %0.5> | %2> | 96 | 1.86 | C |
| after | 84.05±2 | 0.5%> | 2%> | 98 | 0.55 | A |
| 9 months | 89.32±4 | 0.5%> | 2%> | 98 | 0.46 | B |
| | 93.09±4.2 | 0.5%> | 2%> | 94 | 0.48 | C |
| After | 85.48±2.1 | 0.5%> | 2%> | 100 | 1.72 | A |
| 1 Year | 86.63±5 | 0.5%> | 2%> | 98 | 1.33 | B |
| | 89.32±4.3 | 0.5%> | 2%> | 96 | 1.45 | C |

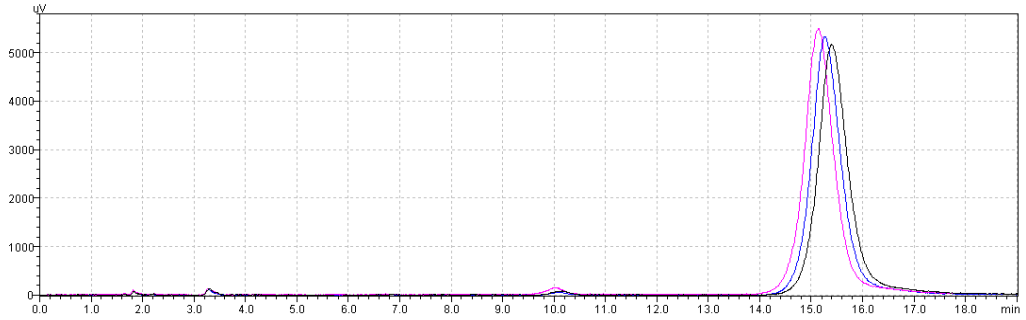


**Fig. 4: Shows After one year, assay of A(pink), BAL(blue), C(black)**

**Verification Results**

The resolution factor of the drug peak from the nearest peak was more than 3 and for any impurity peak from another near peak was more than 3, indicated no interference from excipients, impurities and assured that the peak response was due to a single component only[19]. The peak purity index was close to 1 and for system suitability RSD was < 2% for triplicates, and T.P were >1000 for the assay test and > 3000 for the dissolution test.

**CONCLUSION**

The effect of non hygroscopic excipients was clear as the cornerstone in all formulas. The impact of the L-leucine or film coating on drug stabiltiy was comparable. Moreover the last choice was more important, the packaging with aluminum was more effective in comparison with pvdc package and played the greatest role in drug protection against moisture transit to sensitive drugs, and in order to achieve a stable finished drug product.

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