Stability Report	
Stress Testing and Long-Term Testing of BIWG 98 SE tablets (phase I)	Number **SR 2001-01-01-01** Date **00. 00. 0000** Page **1 of 37**

Responsible Company	Internal Archive Number
Successful Pharma KG Biberach	

Responsible:

Analytical Sciences Department

Drug Product Analysis Laboratory AZ

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1. Summary

1.1. Stability results

The Stability Report comprises the stability data of Stress (accelerated)- and Long-Term Testing, performed to derive the minimum shelf-life (period of use) for clinical trial batches in phase I.

Three laboratory batches of BIWG 98 SE tablets with 10 mg, 40 mg, 120 mg were investigated. The analytical procedures were stability indicating and orientationally validated.

The following influencing factors were investigated: moisture, temperature, moisture + temperature, storage conditions of climatic zone II.

The samples have been stored in open containers at 25°C/60 % r.h. for two weeks, in 50 ml glass container with twist-off closure at 40°C up to 1.5 months, in 50 ml glass container with twist-off closure and polypropylene tubes with polyethylene closure at 25°C/60 % r.h. up to 3 months.

During the open storage the tablets had adsorbed about 2 % water which caused a decrease in hardness (resistance to crushing) and a slight decrease in dissolution rate.

At the subsequent comparative storage of the samples without and with 2 % adsorbed water no further change took place at all test attributes.

The minimum shelf-life of 3 months derived from the data of the stress investigations was confirmed by the results of the long-term testing up to 3 months.

An overview on the analytical results is given in the following table.

Summary of the analytical results

Influencing factor	**Strength**	**Container Closure system**	**Storage conditions** [°C][% r.h.]	**Storage time**	**Test attributes**	**Analytical results**
moisture	10 mg	open container	25 / 60	2 weeks	appearance	no change
					average mass	**+ 2 %**
					disintegration time	no significant change
					dissolution rate	**slight decrease**
					hardness	**decrease**
	40 mg	open container	25 / 60	2 weeks	appearance	no change
					average mass	**+ 2.1 %**
					disintegration time	no significant change
					dissolution rate	**slight decrease**
					hardness	**decrease**
	120 mg	open container	25 / 60	2 weeks	appearance	no change
					average mass	**+ 1.8 %**
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	**decrease**
temperature	10 mg 40 mg 120 mg	50 ml glass container	40 / -	6 weeks	appearance	no change
					average mass	no change
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	no significant change
					degradation of BIWG 98 SE	no degradation
					assay of BIWG 98 SE	no fall in assay

Summary of the analytical results

Influencing factor	**Strength**	**Container Closure system**	**Storage conditions** [°C/%r.h]	**Storage period**	**Test attributes**	**Analytical results**
moisture and temperature (open storage 25°C/60 % 10 mg +2% 40 mg +2.1% 120 mg +1.8%)	10 mg 40 mg 120 mg	50 ml glass container with twist-off closure	40 / -	6 weeks	appearance	no change
					average mass	no change
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	no significant change
					degradation of BIWG 98 SE	no degradation
					assay of BIWG 98 SE	no fall in assay
storage conditions of climatic zone II	10 mg 40 mg 120 mg	50 ml glass Container with twist -off closure, Polypropylene tube with Polyethylene closure lene closure	25 / 60	12 weeks	appearance	no change
					average mass	no change
					disintegration time	no significant change
					dissolution rate	no significant change
					hardness	no significant change
					degradation of BIWG 98 SE	no degradation
					assay of BIWG 98 SE	no fall in assay

The data of dissolution rate and assay of BIWG 98 SE are also presented graphically.

The different strengths of 10 mg, 40 mg, 120 mg had no influence on the stability. Therefore the conclusions can be extended to all further strengths.

The conclusions are as follows:

1.2. Stability and packaging information

The following minimum shelf-life for clinical trial batches phase I in the climatic zones I and II was derived:

Minimum shelf life phase I		
Container closure system	**Climatic zone**	**Minimum shelf life (period of use)**
Glass bottle with screw cap, Polypropylene tube with polyethylene closure Applicable are further: HDPE bottle with HDPE closure HDPE closure Aluminium blister	II	3 months

Storage instructions: none

The derived minimum shelf-life is applied to all clinical batches and all strengths in clinical phase I.

2. Introduction

The label for the investigational medical products should include the period of use (minimum shelf-life) as applicable in months/years, according to the Annex to the EU Guide to Good Manufacturing Practice.

This information must be available before the packaging of the clinical trial batches.

Stress investigations were performed, a procedure well accepted by the authorities.

To include all test attributes in the stability prediction two aspects have to be considered concerning the performance of the stress tests.

- Storage conditions

  A distinction must be drawn between storage for

  - organoleptic and physico-chemical stability, where the laws of reaction kinetics do not apply,

  - chemical stability, where the laws of reaction kinetics may be applicable.

- Selection of container closure systems

  At higher temperatures desorption and loss of moisture occurs. Unless packaging material impermeable to water vapour are used for stress tests with solid dosage forms the samples lose moisture and the results are not suitable for a prediction.

For the phase I of the BIWG 98 SE tablets a series of strengths (10 mg, 20 mg, 40 mg, 60 mg, 80 mg, 120 mg) were intended for investigation. Therefore bracketing was applied for the stress tests. However, not only the extremes, 10 mg and 120 mg but also 40 mg were included in the stress test.

A minimum shelf-life of 3 months was required therefore the samples were stressed for 1.5 months at 40°C to derive the period of use. For later confirmation samples were stored at 25°C/60 % r.h., the condition for climatic zone II.

3. Material and Methods

3.1. Composition

	mg/tablet	mg/tablet	mg/tablet
BIWG 98 SE	10.000	40.000	120.000
Excipients:			
1.....			
2.....			
3			
4			
5			
6			
	60.000	**240.000**	**720.000**

3.2. Batch information

The three batches have been manufactured in the Development Laboratory in laboratory scale of 8.4 kg.

Batch No. / (Strength)	P95004 / (10 mg)	P95005 / (40 mg)	P95006 / (120 mg)
Manufacturer	Successful Pharma KG Biberach		
Date of manufacture	June 0000		
Site of manufacture	Development Laboratory		
Scale of manufacture	Laboratory Scale		
Batch size	8.4 kg		
Active ingredient	BIWG 98 SE		
Batch No.	S95001	S95001	S95002
Manufacturer	Successful Pharma KG Biberach		

3.3. Container closure system

The stress samples were packed in the standard packaging material for stress tests with solid dosage forms, 50 ml glass container with twist-off closure. This packaging material was selected because a tight container is necessary to prevent the loss of moisture during storage at the stress temperatures.

The samples for long-term testing were packed additionally in polypropylene tubes with polyethylene closure, a standard packaging material for clinical trial samples.

3.4. Test attributes

For the stress testing the attributes of BIWG 98 SE tablets were investigated

- which are potentially susceptible to change during the course of storage,
- which are likely to influence quality, safety and efficacy.

The following test attributes had been selected:

Appearance, average mass, disintegration time, dissolution rate, hardness (resistance to crushing), degradation of BIWG 98 SE, assay of BIWG 98 SE.

3.5. Analytical Procedures

The analytical procedures were stability indicating and orientationally validated. This includes: Specificity, linearity, reporting threshold, robustness. Since three strengths were investigated the orientational validation had been performed as follows:

The final concentration of the analyte is the same after sample preparation therefore the validation was limited to the 10 mg tablets.

The most important validation criteria are indicated:

Specificity:	Specificity was demonstrated by separating the drug substance from the degradation product BIWG 98 D1 and the two artificial degradation products BIWG 98 O, BIWG 98 L.
Reporting threshold:	0.1 % $\triangleq$ reporting threshold according to the ICH Guideline "Impurities in New Drug Products". Each degradation product > 0.1 % can be quantified.

The test attributes, the analytical procedures, the specifications are summarized in the:

"Preliminary Testing Specifications for Release and Stability Testing of BIWG 98 SE tablets 10 mg to 120 mg No. PTSDP 910-A-01/01".

For all samples the same testing specification was applied.

3.6. Test attributes and Orientational acceptance criteria

Test attributes	Orientational acceptance criteria
Appearance	Round, white to off-white tablets
Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %
Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)
Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2 (S3 is excluded to be accepted in Europe)
Hardness (resistance to crushing)	$\bar{x}_{10}$ not less than 25 N
Degradation of BIWG 98 SE	- BIWG 98 D1 not more than 1.0 % $\triangleq$ 1.13 % degraded BIWG 98 SE, - any unspecified degradation product up to 0.2 %, - total degradation products not more than 1.3 % $\triangleq$ 1.5 % degraded BIWG 98 SE
Assay of BIWG 98 SE	93 % - 105 % of stated content

3.7. Stability test protocols

3.7.1. Organoleptic and physico-chemical stress testing

Batch No.	Strength	Container closure system	Storage conditions	Storage period, Testing frequency [weeks]	Analytical procedure
P95004	10 mg	open container	25°C/60%	0, 2	PTSDP 910-A-001/01
P95007	40 mg	open container	25°C/60%	0, 2	PTSDP 910-A-001/01
P95009	120 mg	open container	25°C/60%	0, 2	PTSDP 910-A-001/01

3.7.2. Chemical stress testing

Batch No.	Strength	Container closure system	Pretreat-ment	Storage conditions	Storage period, Testing frequency [weeks]	Analytical procedure
P95004	10 mg	50 ml glass container with twist-off closure	none	40°C	0, 2, 4, 6	PTSDP 910-A-01/01
			25°C/60%	40°C	0, 2, 4, 6	PTSDP 910-A-01/01
P95007	40 mg	50 ml glass container with twist-off closure	none	40°C	0, 2, 4, 6	PTSDP 910-A-01/01
			25°C/60%	40°C	0, 2, 4, 6	PTSDP 910-A-01/01
P95009	120 mg	50 ml glass container with twist-off closure	none	40°C	0, 2, 4, 6	PTSDP 910-A-01/01
			25°C/60%	40°C	0, 2, 4, 6	PTSDP 910-A-01/01

3.7.3. Long-term testing

Batch No.	Strength	Container closure system	Storage conditions	Storage period, Testing frequency [weeks]	Analytical procedure
P95004	10 mg	50 ml glass container with twist-off closure	25°C/60%	12	PTSDP 910-A-01/01
		PP-tubes with PE closure	25°C/60%	12	PTSDP 910-A-01/01
P95007	40 mg	50 ml glass container with twist-off closure	25°C/60%	12	PTSDP 910-A-01/01
		PP-tubes with PE closure	25°C/60%	12	PTSDP 910-A-01/01
P95009	120 mg	50 ml glass container with twist-off closure	25°C/60%	12	PTSDP 910-A-01/01
		PP-tubes with PE closure	25°C/60%	12	PTSDP 910-A-01/01

4. Results and Evaluation

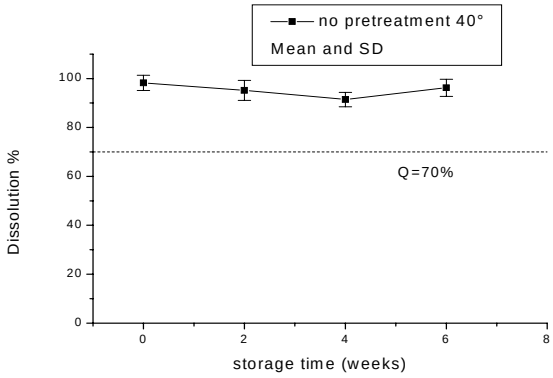
4.1. Graphic of test results

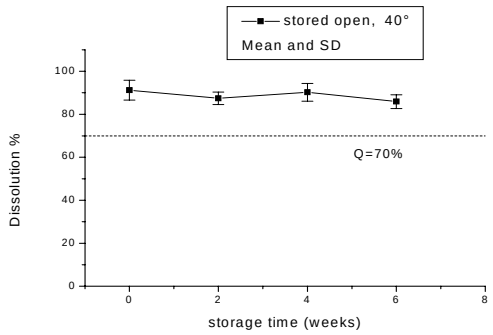
Batch No.: P95004 **(10 mg)**

Container closure system: 50 ml glass container with twist-off closure

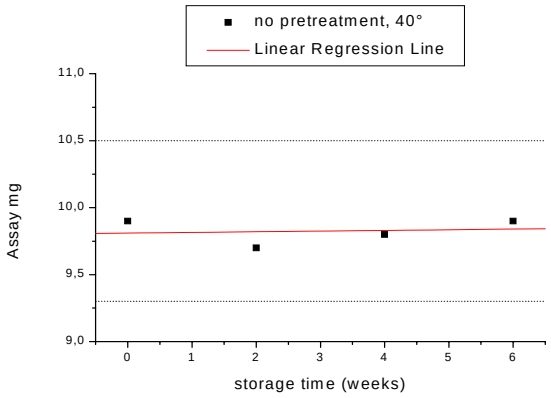
Storage time [weeks]	Storage conditions 40°C/--	
	no pre-treatment	stored open (+ 2.0 %) at 25°C/60 % r.h.

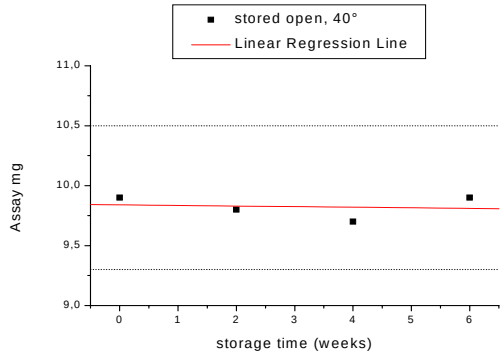
Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2





Assay of BIWG 98 SE	93 % - 105 % (9.3 - 10.5 mg)



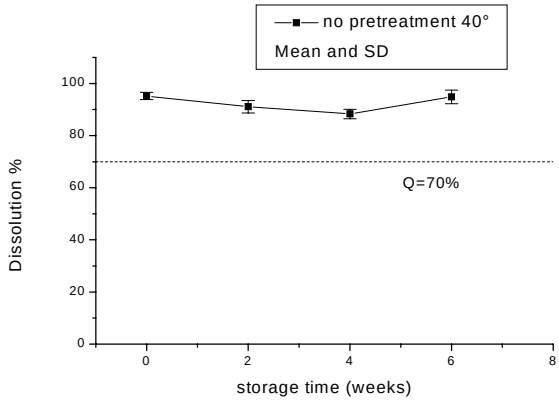


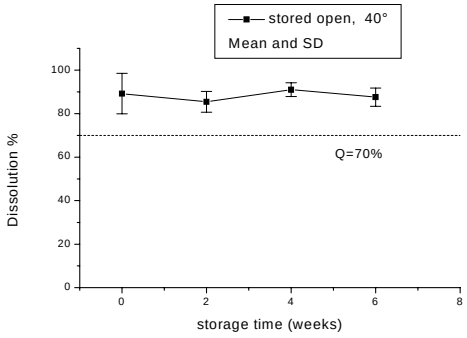
Batch No.: P95007 **(40 mg)**

Container closure system: 50 ml glass container with twist-off closure

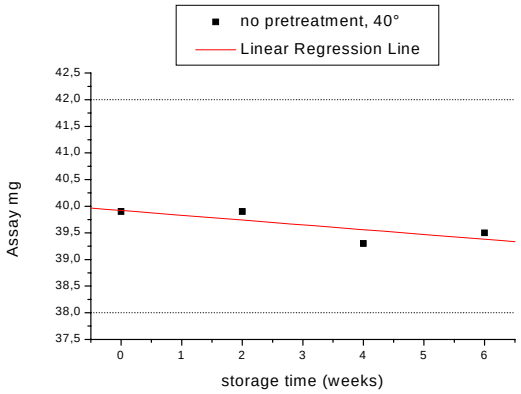
Storage time	**Storage conditions**	
[weeks]	40°C/--	
	no pre-treatment	stored open (+ 2.1 %) at 25°C/60 % r.h.

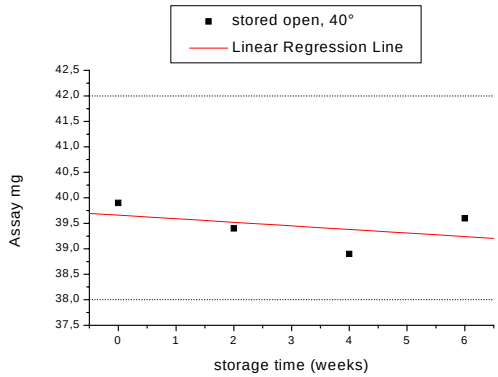
Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2





Assay of BIWG 98 SE	93 % - 105 % (37.2 - 42.0 mg)

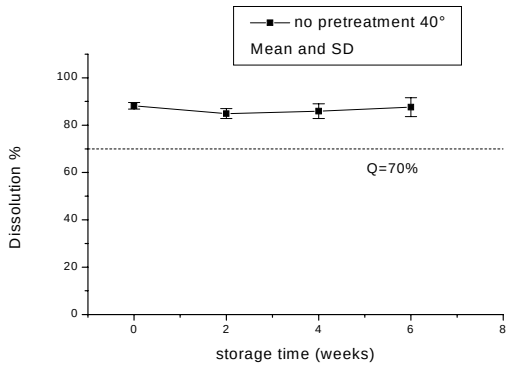


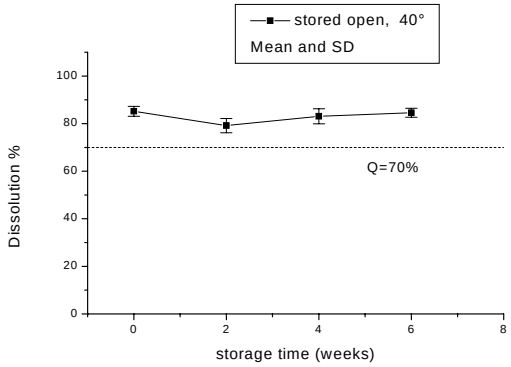


Batch No.: P95009 **(120 mg)** **Container closure system:** 50 ml glass container with twist-off closure

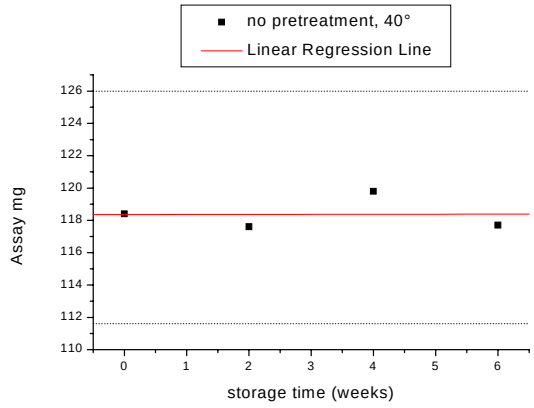
Storage time [weeks]	Storage conditions 40°C/--
no pre-treatment	stored open (+ 1.8 %) at 25°C/60 % r.h.

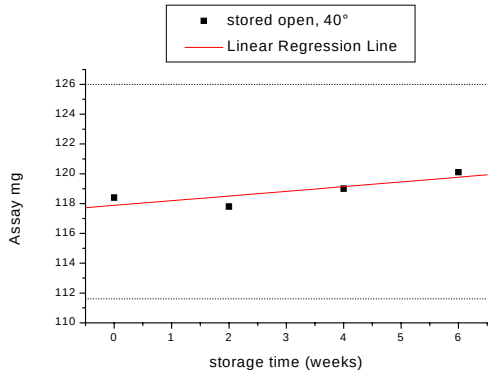
Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2





Assay of BIWG 98 SE	93 % - 105 % (111.6 - 126.0 mg)





4.2. Test results

4.2.1. Organoleptic and physico-chemical stress testing

Batch No.: P95004 **(10 mg)** **Container closure system:** open container

Storage time [weeks]	Storage conditions 25°C/60%

Appearance	Round, white to off-white tablets
0	round, white to off-white tablets
2	unchanged

Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %
0	60.1 mg
2	61.3 mg (+ 2.0 %)

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)
0	$\bar{x}_6$ 3.1 min; RSD 28.9 %
2	4.0 min; 18.5 %

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2
0	$\bar{x}_6$ 98.2 %; RSD 3.1 %
12	91.2 %; 2.9 %

Hardness	$\bar{x}_{10}$ not less than 25 N
0	$\bar{x}_{10}$ 54.0 N; RSD 7.8 %
2	38.1 N; 2.9 %

Batch No.: P95007 **(40 mg)** **Container closure system:** open container

Storage time	Storage conditions
[weeks]	25°C/60%

Appearance	Round, white to off-white tablets
0	round, white to off-white tablets
2	unchanged

Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %
0	244.5 mg
2	249.6 mg (+ 2.1 %)

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)
0	$\bar{x}_6$ 4.5 min; RSD 20.4 %
2	4.2 min; 25.6 %

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2
0	$\bar{x}_6$ 95.2 %; RSD 1.41 %
2	89.2 %; 2.5 %

Hardness	$\bar{x}_{10}$ not less than 25 N
0	$\bar{x}_{10}$ 61.4 N; RSD 10.2 %
2	40.2 N; 9.3 %

Batch No.: P95009 **(120 mg)** **Container closure system:** open container

Storage time	Storage conditions
[weeks]	25°C/60%

Appearance	Round, white to off-white tablets
0	round, white to off-white tablets
2	unchanged

Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %
0	721.2 mg
2	734.2 mg (+ 1.8 %)

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)
0	$\bar{x}_6$ 5.6 min; RSD 20.4 %
2	5.9 min; 33.1 %

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2
0	$\bar{x}_6$ 88.2 %; RSD 1.4 %
12	85.2 %; 2.1 %

Hardness	$\bar{x}_{10}$ not less than 25 N
0	$\bar{x}_{10}$ 75.4 N; RSD 12.7 %
2	60.3 N; 6.4 %

4.2.2. Chemical stress testing

Batch No.: P95004 **(10 mg)** **Container closure system:** 50 ml glass container with twist-off closure

Storage time [weeks]	Storage conditions 40°C/--
no pre-treatment	stored open (+ 2.0 %) at 25°C/60 % r.h.

Appearance	Round, white to off-white tablets	
0	round, white to off-white tablets	round, white to off-white tablets
2	unchanged	unchanged
4	unchanged	unchanged
6	unchanged	unchanged

Average mass	x_{20} (initial value) + 2.5 %	
0	60.1 mg	61.3 mg
2	59.8 mg	60.9 mg
4	60.6 mg	61.2 mg
6	61.2 mg	62.0 mg

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)	
0	$\bar{x}_6$ 3.1 min; RSD 28.9 %	$\bar{x}_6$ 4.0 min; RSD 18.5 %
2	3.4 min; 25.2 %	4.1 min; 17.5 %
4	3.0 min; 18.4 %	3.8 min; 23.5 %
6	3.5 min; 19.9 %	3.9 min; 19.4 %

Batch No.: P95004 **(10 mg)** **Container closure system:** 50 ml glass container with twist-off closure

Storage time	**Storage conditions**	
[weeks]	40°C/--	
	no pre-treatment	stored open (+ 2.0 %) at 25°C/60 % r.h.

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2	
0	$\bar{x}_6$ 98.2 %; RSD 3.1 %	$\bar{x}_6$ 91.2 %; RSD 4.6 %
2	95.2 %; 4.1 %	87.4 %; 2.9 %
4	91.4 %; 2.9 %	90.2 %; 4.1 %
6	96.2 %; 3.5 %	85.9 %; 3.2 %

Hardness	x_{10} not less than 25 N	
0	$\bar{x}_{10}$ 54.0 N; RSD 7.8 %	$\bar{x}_{10}$ 38.1 N; RSD 2.9 %
2	56.4 N; 8.2 %	34.2 N; 3.4 %
4	49.8 N; 6.9 %	36.4 N; 4.2 %
6	51.9 N; 8.0 %	39.1 N; 5.6 %

Degradation of BIWG 98 SE	- BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, - any unspecified degradation product up to 0.2 %, - total degradation products not more than 1.3 % 1.5 % degraded BIWG 98 SE	
0	no degradation	no degradation
2	no degradation	no degradation
4	no degradation	no degradation
6	no degradation	no degradation

Batch No.: P95004 **(10 mg)** **Container closure system:** 50 ml glass container with twist-off closure

Storage time	**Storage conditions**	
[weeks]	40°C/--	
	no pre-treatment	stored open (+ 2.0 %) at 25°C/60 % r.h.

Assay of BIWG 98 SE	93 % - 105 % (9.3 - 10.5 mg)	
0	9.9 mg	9.9 mg
2	9.7 mg	9.8 mg
4	9.8 mg	9.7 mg
6	9.9 mg	9.9 mg

Batch No.: P95007 **(40 mg)** **Container closure system:** 50 ml glass container with twist-off closure

Storage time	**Storage conditions**	
[weeks]	40°C/--	
	no pre-treatment	stored open (+ 2.1 %) at 25°C/60 % r.h.

Appearance	Round, white to off-white tablets	
0	round, white to off-white tablets	round, white to off-white tablets
2	unchanged	unchanged
4	unchanged	unchanged
6	unchanged	unchanged

Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %	
0	244.5 mg	249.6 mg
2	243.8 mg	249.9 mg
4	245.0 mg	248.9 mg
6	244.4 mg	249.5 mg

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)	
0	$\bar{x}_6$ 4.5 min; RSD 20.4 %	$\bar{x}_6$ 4.2 min; RSD 25.6 %
2	4.1 min; 25.4 %	4.6 min; 21.6 %
4	4.8 min; 23.5 %	3.9 min; 29.8 %
6	3.9 min; 18.3 %	4.5 min; 24.3 %

Batch No.: P95007 **(40 mg)** **Container closure system:** 50 ml glass container with twist-off closure

Storage time	**Storage conditions**	
[weeks]	40°C/--	
	no pre-treatment	stored open (+ 2.1 %) at 25°C/60 % r.h.

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2	
0	$\bar{x}_6$ 95.2 %; RSD 1.4 %	$\bar{x}_6$ 89.2 %; RSD 9.3 %
2	91.1 %; 2.4 %	85.4 %; 4.8 %
4	88.3 %; 1.8 %	91.0 %; 3.2 %
6	94.8 %; 2.6 %	87.6 %; 4.2 %

Hardness	x_{10} not less than 25 N	
0	$\bar{x}_{10}$ 61.4 N; RSD 10.2 %	$\bar{x}_{10}$ 40.2 N; RSD 9.3 %
2	59.3 N; 8.4 %	41.2 N; 6.7 %
4	57.2 N; 6.2 %	39.8 N; 7.6 %
6	59.4 N; 4.9 %	38.6 N; 8.2 %

Degradation of BIWG 98 SE	- BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, - any unspecified degradation product up to 0.2 %, - total degradation products not more than 1.3 % 1.5 % degraded BIWG 98 SE	
0	no degradation	no degradation
2	no degradation	no degradation
4	no degradation	no degradation
6	no degradation	no degradation

Batch No.: P95007 **(40 mg)** **Container closure system:** 50 ml glass container with twist-off closure

Storage time	**Storage conditions**	
[weeks]	40°C/--	
	no pre-treatment	stored open (+ 2.1 %) at 25°C/60 % r.h.

Assay of BIWG 98 SE	93 % - 105 % (37.2 - 42.0 mg)	
0	39.9 mg	39.9 mg
2	39.9 mg	39.4 mg
4	39.3 mg	38.9 mg
6	39.5 mg	39.6 mg

Batch No.: P95009 **(120 mg)** **Container closure system:** 50 ml glass container with twist-off closure

Storage time	**Storage conditions**	
[weeks]	40°C/--	
	no pre-treatment	stored open (+ 1.8 %) at 25°C/60 % r.h.

Appearance	Round, white to off-white tablets	
0	round, white to off-white tablets	round, white to off-white tablets
2	unchanged	unchanged
4	unchanged	unchanged
6	unchanged	unchanged

Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %	
0	721.2 mg	734.2 mg
2	724.1 mg	731.9 mg
4	720.9 mg	735.1 mg
6	722.0 mg	732.6 mg

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)	
0	$\bar{x}_6$ 5.6 min; RSD 20.4 %	$\bar{x}_6$ 5.9 min; RSD 33.1 %
2	4.9 min; 25.6 %	5.6 min; 28.4 %
4	5.9 min; 23.5 %	6.2 min; 23.5 %
6	4.8 min; 28.6 %	6.1 min; 19.8 %

Batch No.: P95009 **(120 mg)** **Container closure system:** 50 ml glass container with twist-off closure

Storage time [weeks]	**Storage conditions** 40°C/--	
	no pre-treatment	stored open (+ 1.8 %) at 25°C/60 % r.h.

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2	
0	$\bar{x}_6$ 88.2 %; RSD 1.4 %	$\bar{x}_6$ 85.2 %; RSD 2.1 %
2	84.9 %; 2.1 %	79.2 %; 3.0 %
4	85.9 %; 3.1 %	83.1 %; 3.2 %
6	87.6 %; 4.0 %	84.6 %; 1.9 %

Hardness	x_{10} not less than 25 N	
0	$\bar{x}_{10}$ 75.0 N; RSD 12.7 %	$\bar{x}_{10}$ 40.2 N; RSD 9.3 %
2	72.9 N; 14.1 %	61.4 N; 6.0 %
4	76.8 N; 12.2 %	58.0 N; 3.2 %
6	73.8 N; 11.1 %	62.4 N; 4.2 %

Degradation of BIWG 98 SE	- BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, - any unspecified degradation product up to 0.2 %, - total degradation products not more than 1.3 % 1.5 % degraded BIWG 98 SE	
0	no degradation	no degradation
2	no degradation	no degradation
4	no degradation	no degradation
6	no degradation	no degradation

Batch No.: P95009 **(120 mg)** **Container closure system:** 50 ml glass container with twist-off closure

Storage time [weeks]	**Storage conditions** 40°C/--
no pre-treatment	stored open (+ 1.8 %) at 25°C/60 % r.h.

Assay of BIWG 98 SE	93 % - 105 % (111.6 - 126.0 mg)	
0	118.4 mg	118.4 mg
2	117.6 mg	117.8 mg
4	119.8 mg	119.0 mg
6	117.7 mg	120.1 mg

4.2.3. Long-term testing

Batch No.: P95004
(10 mg)

Container closure system
1. 50 ml glass container with twist-off closure
2. Polypropylene tubes with Polyethylene closure

Storage time	**Storage conditions**	
[weeks]	25°C/60 %	
	Packaging material 1	Packaging material 2

Appearance	Round, white to off-white tablets	
0	round, white to off-white tablets	round, white to off-white tablets
12	unchanged	unchanged

Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %	
0	60.1 mg	61.3 mg
12	61.2 mg	60.5 mg

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)	
0	$\bar{x}_6$ 3.1 min; RSD 28.9 %	$\bar{x}_6$ 3.1 min; RSD 28.9 %
12	4.0 min; 23.5 %	3.2 min; 22.2 %

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2	
0	$\bar{x}_6$ 98.2 %; RSD 3.1 %	$\bar{x}_6$ 98.2 %; RSD 3.1 %
12	95.2 %; 4.1 %	96.9 %; 2.9 %

Hardness	$\bar{x}_{10}$ not less than 25 N	
0	$\bar{x}_{10}$ 54.0 N; RSD 7.8 %	$\bar{x}_{10}$ 54.0 N; RSD 7.8 %
12	56.1 N; 6.8 %	53.9 N; 5.2 %

Batch No.: P95004
(10 mg)

Container closure system
1. 50 ml glass container with twist-off closure
2. Polypropylene tubes with Polyethylene closure

Storage time	**Storage conditions**	
[weeks]	25°C/60 %	
	Packaging material 1	Packaging material 2

Degradation of BIWG 98 SE	- BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, - any unspecified degradation product up to 0.2 %, - total degradation products not more than 1.3 % 1.5 % degraded BIWG 98 SE	
0	no degradation	no degradation
12	no degradation	no degradation

Assay of BIWG 98 SE	93 % - 105 % (9.3 - 10.5 mg)	
0	9.9 mg	9.9 mg
12	9.7 mg	9.8 mg

Batch No.: P95007
(40 mg)

Container closure system
1. 50 ml glass container with twist-off closure
2. Polypropylene tubes with Polyethylene closure

Storage time [weeks]	**Storage conditions** 25°C/60 %	
	Container closure system 1	Container closure system 2

Appearance	Round, white to off-white tablets	
0	round, white to off-white tablets	round, white to off-white tablets
12	unchanged	unchanged

Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %	
0	244.5 mg	244.5 mg
12	243.9 mg	245.1 mg

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)	
0	$\bar{x}_6$ 4.5 min; RSD 20.4 %	$\bar{x}_6$ 4.5 min; RSD 20.4 %
12	5.1 min; 23.5 %	4.4 min; 21.8 %

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2	
0	$\bar{x}_6$ 95.2 %; RSD 1.4 %	$\bar{x}_6$ 95.2 %; RSD 1.4 %
12	93.8 %; 2.1 %	94.0 %; 1.9 %

Hardness	$\bar{x}_{10}$ not less than 25 N	
0	$\bar{x}_{10}$ 61.4 N; RSD 10.2 %	$\bar{x}_{10}$ 61.4 N; RSD 10.2 %
12	59.5 N; 7.9 %	58.7 N; 8.8 %

Batch No.: P95007
(40 mg)

Container closure system
1. 50 ml glass container with twist-off closure
2. Polypropylene tubes with Polyethylene closure

Storage time	**Storage conditions**	
[weeks]	25°C/60 %	
	Container closure system 1	Container closure system 2
Degradation of BIWG 98 SE	- BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, - any unspecified degradation product up to 0.2 %, - total degradation products not more than 1.3 % 1.5 % degraded BIWG 98 SE	
0	no degradation	no degradation
12	no degradation	no degradation

Assay of BIWG 98 SE	93 % - 105 % (37.2 - 42.0 mg)	
0	39.9 mg	39.9 mg
12	39.6 mg	39.7 mg

Batch No.: P95009 **(120 mg)**

Container closure system
1. 50 ml glass container with twist-off closure
2. Polypropylene tubes with Polyethylene closure

Storage time	**Storage conditions**	
[weeks]	25°C/60 %	
	Container closure system 1	Container closure system 2

Appearance	Round, white to off-white tablets	
0	round, white to off-white tablets	round, white to off-white tablets
12	unchanged	unchanged

Average mass	$\bar{x}_{20}$ (initial value) + 2.5 %	
0	721.2 mg	721.2 mg
12	724.2 mg	720.9 mg

Disintegration time	Not more than 15 minutes (each individual value $\leq$ 15 min)	
0	$\bar{x}_6$ 5.6 min; RSD 20.4 %	$\bar{x}_6$ 5.6 min; RSD 20.4 %
12	6.8 min; 23.5 %	5.9 min; 18.6 %

Dissolution rate	Not less than 70 % (Q) after 30 minutes, complies with USP stages S1 and S2	
0	$\bar{x}_6$ 88.2 %; RSD 1.4 %	$\bar{x}_6$ 88.2 %; RSD 1.4 %
12	85.2 %; 2.9 %	84.9 %; 3.2 %

Hardness	$\bar{x}_{10}$ not less than 25 N	
0	$\bar{x}_{10}$ 75.0 N; RSD 12.7 %	$\bar{x}_{10}$ 75.0 N; RSD 12.7 %
12	69.2 N; 11.2 %	78.0 N; 9.4 %

Batch No.: P95009
(120 mg)

Container closure system
1. 50 ml glass container with twist-off closure
2. Polypropylene tubes with Polyethylene closure

Storage time	**Storage conditions**	
[weeks]	25°C/60 %	
	Container closure system 1	Container closure system 2
Degradation of BIWG 98 SE	- BIWG 98 D1 not more than 1.0 % 1.13 % degraded BIWG 98 SE, - any unspecified degradation product up to 0.2 %, - total degradation products not more than 1.3 % 1.5 % degraded BIWG 98 SE	
0	no degradation	no degradation
12	no degradation	no degradation

Assay of BIWG 98 SE	93 % - 105 % (111.6 - 126.0 mg)	
0	118.4 mg	118.4 mg
12	120.1 mg	118.2 mg

4.3. Evaluation

The stability report comprises the results of three batches of BIWG 98 SE tablets 10, 40, 120 mg. They form a homologous series, the ratio of the active ingredient and the excipients stays the same.

The batches have been manufactured in the laboratories of the pharmaceutical development. The samples have been stressed at 40°C up to 1.5 months and stored for confirmation at 25°C/60 % r.h. up to 3 months.

In this case 40°C is called stress temperature and not accelerated temperature.

4.3.1. Stress Testing

4.3.1.1. Organoleptic and physico-chemical stability

To investigate the organoleptic and physico-chemical stability, the samples have been kept for two weeks in open containers at the storage condition for climatic zone II 25°C/60 % r.h. to examine the maximal influence of water. The samples adsorbed 2 % water. The appearance and disintegration time were unchanged, the hardness decreased, the dissolution rate decreased slightly. the chemical stability is not influenced after 2 weeks storage at 25°C, therefore the samples were not analysed for decomposition and assay.

4.3.1.2. Chemical stability

To investigate the chemical stability the tablets were stored at 40°C up to 1.5 months. No decomposition or fall in assay demonstrated the good chemical stability. Also the organoleptic and physico-chemical criteria indicated no significant change. To include the possible influence of water on the chemical stability, samples which had adsorbed 2 % water were stored in parallel with the untreated tablets in 50 ml glass containers with twist-off closure at 40°C up to 1.5 months. No decomposition or fall in assay, no significant change of the organoleptic and physico-chemical criteria.

4.3.2. Long-term Testing

The samples packed in 50 ml glass container with twist-off closure and polypropylene tubes with polyethylene closure were stored at 25°C/60 % r.h., the storage condition of the climatic zone II, up to 3 months to confirm the minimum shelf-life of 3 months, derived from the results of the stress investigations. All data were within the specifications, no change had taken place.

5. Conclusion

The BIWG 98 SE tablets are a stable formulation, the different strengths have no influence on the stability, the results of 10 mg, 40 mg, 120 mg are comparable. During open storage at 25°C/60 % r.h. the tablets adsorbed 2 % water which caused a decrease in hardness and initially a slight decrease in dissolution rate. Both changes were not enforced during storage for 1.5 months at 40°C in tight containers.

The derived minimum shelf-life of 3 months was confirmed by the results of long-term testing at 25°C/60 % r.h. for 3 months.

The following container closure systems can be recommended:

- Glass bottle with screw cap
- Polypropylene tubes with polyethylene closure
- Polyethylene bottles
- Aluminium blisters

No storage instruction is required.