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Research Article

Formulation and *in vitro* evaluation of inosine acedoben dimepranol tablets

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Abstract

The present work was carried out to formulate and evaluate immediate release tablets of Inosine Acedoben Dimepranol (IAD). Tablets were prepared by wet granulation process to overcome the poor compression properties of IAD powder and produce high-dose tablets. Various type of binders and disintegrants like Povidone K-30, K-25, wheat starch, mannitol were used to prepare some series of tablets. Granules were evaluated for pre-compression parameters and tablets were evaluated for post- compression parameters. The composition batch № IAD L03 was the best for producing IAD 500 mg tablets. The optimal lubricant is glycerol dibehenate at a concentration of 3.08%. Optimized formulation was evaluated for *in-vitro* dissolution test. Stability studies were performed for the selected composition.

Keywords

Inosine Acedoben Dimepranol, tablets, binders, dissolution

Introduction

The active substance Inosine Acedoben Dimepranol (INN) (IAD), also known as Inosine pranobex and Methisoprinol, is an immunomodulator indicated for the treatment of viral infections such as influenza /viral respiratory infections, herpes simplex and herpes zoster, viral hepatitis, infectious diseases (rubella, chickenpox, measles, influenza) and others according to the summary of product characteristics (SmPC) Isoprinosine 500 mg tablets (Sliva et al. 2019).

The drug was developed by Newport Pharmaceuticals in the 1970s and distributed in more than 80 countries under the trademarks Isoprinosine, Inmunovir and Viruxan (owned by Newport). The active substance is a compound (complex) of inosine (1,9-dihydro-9-Dribofurasonyl-6H-purin-6-one) and a salt of 4-acetamidobenzoic acid with N, N dimethylamino-2-propanol in a molar ratio of 1: 3. It is a crystalline powder with a white to cream color and a characteristic odor, freely soluble in water, sparingly soluble in methanol, acetone, ethanol (Gordon 1974).

The active ingredient is not included in any pharmacopoeia.

When administered orally in men, Isoprinosine is rapidly and completely absorbed (≥ 90%) from the gastrointestinal tract and appears in the blood. In human subjects following a 1 g oral dose of Isoprinosine, the following plasma levels were found for DIP [N,N-dimethylamino-2-propanol] and PAcBA [p-acetamidobenzoic acid], respectively: 3.7μg/ml (2 hours) and 9.4μg/ml (1 hour) (Chen et al. 2013).

Maximum plasma inosine concentrations of the order of 0.6 mg /L were established within 1 hour after an oral dose of 1.5 g in healthy volunteers. Plasma concentrations cannot be determined approximately 2 hours after dosing. Plasma concentrations of inosine in healthy volunteers were

maintained in the range of 100–1000 ng /ml after therapeutic doses, with no increase in correlation with dose increase.

There are no data for classification of IAD according to the Biopharmaceutics Classification System (BCS).

There are no published articles on the composition and production process of IAD tablets with immediate release of the active substance.

Patent ITMI932019 describes only the composition of IAD tablets without process: mannitol, starch, polyvinylpyrrolidone, magnesium stearate (Garzia Stefano and Brugola Luciano (1993).

According to the SmPC Isoprinosine 500 mg tablets, the composition is as follows: mannitol, wheat starch, povidone, magnesium stearate.

The aim of this work is to develop a stable product with fixed properties in the form of oral tablets, containing Inosine Acedoben Dimepranol 500 mg as active substance and with immediate release of the active substance.

Materials and methods

Materials

Inosine Acedoben Dimepranol (ABC Farmaceutici S.p.A., Italy), wheat starch (Roquette), povidone K25, K30 (Kollidon25, 30 BTC Europe GmbH/ BASF), mannitol (Pearlitol 200 SD, Roquette), glycerol dibehenate (Compritol 888 ATO, GATTEFOSSE), magnesium stearate (Peter Greven); all excipients meet the requirements of Ph. Eur.

Methods

Preparation of tablets

The compositions of a series of laboratory batches are presented in Tables 3, 4.

The size of the laboratory batches is 2 000 tablets (1300 g).

The wet granulation method is used for all batches.

- The ingredients are measured according to the recipe and sieved through a sieve with a pore size of 0.8 mm.
- Preparation of inosine acedoben dimepranol granules

Inosine acedoben dimepranol, wheat starch (70.73% of the total) and povidone are loaded into the planetary lab mixer. The mass is mixed dry for 5 minutes. The resulting dry mixture is moistened with the water-alcohol mixture. The solvent was added to the mixture over 5 minutes. Finally, mixing was continued for another 5 minutes.

The wet granules are sieved through a granulator equipped with a 2.0 mm sieve.

The wet granules are dried in a chamber dryer at a temperature of up to 50 °C and with a residual moisture of 1.5 ÷ 3.5%.

The dry granules are sieved through a granulator equipped with a 1.6 mm sieve.

- Preparation of a mixture for tableting

Mannitol 200 SD and the rest of the wheat starch were added to the obtained granules and homogenized in a diffusion mixer for 15 minutes. Lubricant was added and homogenized for 5 minutes.

- Tableting

The tablet mixture is compressed on a rotary tablet press (Compacta III, Riva S.A., Argentina) equipped with the following tools and parameters:

Punches: round, flat, diameter 13 mm;

Average mass per tablet 650 mg ± 5.0% (617.5 mg–682.5 mg);

Hardness: target value 100 N (from 70 N to 140 N);

Friability: not more than 1.0%.

Characterization of the finished granules

The granules are evaluated by the "Hausner ratio" method in accordance with the requirements of Ph. Eur. and residual moisture measured at 105 ^{0}C by an apparatus Precisa XM 50 Moisture Analyser.

Hardness measurements

The measurement is performed according to the method of Ph. Eur.

Disintegration time studies

Disintegration test is performed according to the method of Ph. Eur.

Friability

The test is performed according to the method of Ph. Eur.

Assay of inosine acedoben dimepranol in tablets

Two analytical methods have been reported to determine IAD in drug products. These included the TLC method (Dreassi E et al. 1992) and the validated TLC-densitometry method (Mohamed TA 2014).

The following liquid chromatographic method for analysis has been developed and validated.

Reagents:

- Methanol purity for liquid chromatography
- Orthophosphoric acid - p.a.
- Water for chromatography

Reference standard: IAD, working standard.

Chromatography system:

Equipment: A liquid chromatograph with a UV detector with variable wavelength;

Column: Stainless steel column with a length of 150 mm and internal diameter of 4.6 mm;

Stationary phase: Filling of octadecylsilyl silica gel (RP-18) with a particle size of 5 μm (e.g., Inertsil ODS- 3).

Mobile phases:

Mobile phase A: A mixture of 80 volumes of water and 20 volumes of methanol containing 0.1% phosphoric acid.

Mobile phase B: A mixture of 60 volumes of water and 40 volumes of methanol.

Mobile phases were filtered through 0.45 µm millipore filter and degassed.

Chromatography is carried out with the following gradient system:

Chromatographic conditions:

Flow: 2.0 ml/min

Column temperature: 30 °C

Analytical wavelength: 254 nm

Injection volume: 20 µl

Table 1. Gradient mode.

Time (min)	Mobile phase A	Mobile phase B	
2	100	0	isocratic
0.5	0	100	linear gradient
3.5	0	100	isocratic
0.5	100	0	linear gradient
1	100	0	isocratic

Solvent: A mixture of 10 volumes of methanol and 90 volumes of water.

Test solutions: To 0.650 g of the crushed tablet mass, corresponding to 500 mg IAD, 40–50 ml of solvent are added, homogenized, diluted to 100.0 ml with solvent and sonicated for 5 minutes. Cooled and filtered through a 0.45 mm pore size filter (Nylon is suitable). Diluted 1.0 ml of the filtrate to 100.0 ml with the solvent.

Reference solution: 25.0 mg, IAD working standard was dissolved in the solvent and diluted to 50.0 ml with the same solvent. Diluted 1.0 ml of the resulting solution to 10.0 ml with the solvent. The column is conditioned for about 30 minutes on mobile phase A, then 20 ml of the reference solution are introduced six times.

Retention time:

- Inosine - about 1.2 min
- 4-acetamidobenzoic acid salts -about 5.1 min.

After the suitability of the chromatographic system has been established, the test solution is introduced.

The content of inosine and 4-acetamidobenzoic acid salt in mg was calculated.

The total content (X) in mg/tablet is calculated by the formula:

$$X = 0.2405 \times Xi + 0.7595 \times X_{4\text{-acet}}$$

where:

Xi = IAD content, such as inosine, mg/tablet;

$X_{4\text{-acet}}$ = IAD content, such as 4-acetamido benzoic acid salt, mg/tabet.

Solubility study of IAD - Preliminary test

To approximately 690 mg of the sample IAD in a glass-stoppered 10 ml graduated cylinder, increased volumes of solvent at 37 °C are added according to the steps shown in the following table:

Table 2. Solubility study steps.

Solubility data	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Total volume solvent added (ml)	1.0	1.5	2.0	2.5	3.0	3.5
Approximate solubility (mg/ml)						
Approximate solubility (%)						

After each addition of solvent to give the indicated total volume, the mixture is shaken vigorously for 10 min and is visually checked for any undissolved parts of the sample. If, after a total of 10 ml of solvent has been added, the sample or parts of it remain undissolved, the contents of the measuring cylinder is transferred to a 100 ml measuring cylinder which is then filled up with solvent to 100 ml and then shaken. At lower solubility the time required to dissolve IAD can be considerably long (24 h should be allowed). The approximate solubility is given in the table under that volume of added solvent in which complete dissolution of the sample occurs.

Dissolution testing

The dissolution rate of IAD from tablets was studied in 900 ml of dissolving medium with temperature 37 ± 0.5 °C using Ph. Eur. Dissolution Test Apparatus (Model Pharma Test PTWS-MA) with paddle stirrers.

Table 3. Compositions of laboratory batches.

Ingredients mg/tabl	Batch №									
	IAD L01	% w/w	IAD L02	% w/w	IAD L03	% w/w	IAD L04	% w/w	IAD L05	% w/w
Granules										
Inosine Acedoben Dimepranol	500.0	76.92	500.0	76.92	500.0	76.92	500.0	76.92	500.0	76.92
Wheat starch	60.0	9.23	60.0	9.23	60.0	9.23	60.0	9.23	60.0	9.23
Kollidon K25	*10.0*	1.54	*15.0*	2.31	***22.0***	3.38	*26.0*	4.00	–	–
Kollidon K30	–	–	–	–	–	–	–	–	*22.0*	3.38
Ethanol 96%*	18.9		18.9		18.9		18.9		18.9	
Water purified*	18.9		18.9		18.9		18.9		18.9	
Mixture for tableting										
Granules IAD	570.0		575.0		582.0		586.0		582.0	
Mannitol 200 SD	35.0	4.95	30.0	4.62	23.0	3.54	19.0	2.92	23.0	3.54
Wheat starch	25.0	3.85	25.0	3.85	25.0	3.85	25.0	3.85	25.0	3.85
Glycerol dibehenate	20.0	3.08	20.0	3.08	20.0	3.08	20.0	3.08	20.0	3.08
Magnesium stearate	–	–	–	–	–	–	–	–	–	–
Total	650.0	100.0	650.0	100.0	650.0	100.0	650.0	100.0	650.0	100.0

* The solvents evaporate during the production process.

Table 4. Compositions of laboratory batches.

Ingredients mg/tabl	Batch №					
	IAD L06	% w/w	IAD L07	% w/w	IAD L08	% w/w
Granules						
Inosine Acedoben Dimepranol	500.0	76.92	500.0	76.92	500.0	76.92
Wheat starch	60.0	9.23	60.0	9.23	60.0	9.23
Kollidon K25	***22.0***	3.38	***22.0***	3.38	***22.0***	3.38
Kollidon K30	-	-	-	-	-	-
Ethanol 96%*	18.9		18.9		18.9	
Water purified*	18.9		18.9		18.9	
Mixture for tableting						
Granules IAD	582.0		582.0		582.0	
Mannitol 200 SD	33.0	5.08	26.0	4.00	26.0	4.00
Wheat starch	25.0	3.85	25.0	3.85	25.0	3.85
Glycerol dibehenate	-	-	-	-	17.0	2.62
Magnesium stearate	*10.0*	1.54	*7.0*	1.08	-	-
Stearic acid	-	-	*10.0*	1.54		
Total	650.0	100.0	650.0	100.0	650.0	100.0

* The solvents evaporate during the production process.

Test time - 45 min.

Samples of 5 ml were taken after 10, 15, 20, 30 and 45 minutes from each vessel of the apparatus, filtered through a 0.45 μm filter and analyzed on a liquid chromatograph for IAD content.

Dissolution profile experiments were performed under the following conditions: pH 1.2, 4.5, 6.8 and stirrer speeds 50 rpm and 75 rpm.

Evaluation of the results: The amount of IAD released such as Inosine and 4-acetamidobenzoic acid salt from each tablet should be at least 80% (Q + 5%) of the declared.

Factor of similarity

The calculation of the factor of similarity was made according to the requirements of Guideline on the investigation of bioequivalence (CPMP /EWP /QWP/1401/98/ Rev 1/ Corr **).

Stability studies

Tests for stability of samples of the product under accelerated conditions - 40 °C / 75% RH for six months according to the requirements of Note for guidance on stability testing: Stability testing of new drug substances and products (CPMP/ICH/2736/99) were performed.

Results and discussion

The method for wet granulation is chosen, characterized by the ability to formulate high-dose tablets, as it is the case with the developed product. Other reasons are:

- Bulk density increase, which is due to multiple increase in the size of dust particles, which gives them excellent flow properties.
- The binding properties of the powders are improved, whereby they acquire the property of cohesiveness, which is especially important for obtaining quality tablets.

The povidone binder is included in powder form in the granulation mixture and granulated *in situ* by adding the solvent - aqueous alcoholic mixture (Bühler V 2005). This method is preferable in order to optimize the required amount of binder in the granules and to avoid exceeding the saturation limit of the granules (overwetting), especially in the case where the active substance is well soluble in water, such as IAD.

The results of the tested physicochemical parameters of the batches are presented in Tables 5, 6.

Table 5. Results of tested physicochemical parameters.

Tested parameters	Evaluation				
	IAD L01	IAD L02	IAD L03	IAD L04	IAD L05
Bulk density of granules g/ml	0.417	0.455	**0.476**	0.488	0.476
Hausner ratio of granules	1.200	1.222	**1.050**	1.108	1.050
Residual moisture of granules, %	3.0	2.6	**2.4**	2.5	2.1
Average mass per tablet (mg)	650.7	652.4	**650.8**	651.2	653.6
Hardness (N)	50	70	**110**	120	130
n=10; ± SD	± 9.2	± 6.6	**± 7.4**	± 5.4	± 6.7
Disintegration (min)	6.0	6.5	**7.0**	9.50	10.5
Friability (%)	0.84	0.73	**0.51**	0.45	0.42
Defects in the appearance of the tablets, %	2.0	no	**no**	no	no

Table 6. Results of tested physicochemical parameters.

Tested parameters	Evaluation		
	IAD L06	IAD L07	IAD L08
Bulk density of granules g/ml	0.455	0.476	0.476
Hausner ratio of granules	1.048	1.050	1.050
Residual moisture of granules, %	2.4	2.1	2.3
Average mass per tablet (mg)	651.3	650.4	652.8
Hardness (N) n=10; ± SD	55 ± 8.2	75 ± 7.8	102 ± 6.4
Disintegration (min)	10.0	8.0	7.0
Friability (%)	0.86	0.63	0.55
Defects in the appearance of the tablets, %	2.0	1.0	0.5

With regard to the „flow" property of the granules, the „Hausner ratio" data showed all batches have good criterion values except batches № IAD L01 and № IAD L02. The Hausner ratio may be related to the compressibility of powder and values < 1.25 are indicative for good compressibility (Wells 2005). In case of batch № IAD L01, the lowest value of the achieved bulk density of the granules is observed. This characteristic also correlates with the low hardness of the tablets.

As the amount of Povidone K25 binder (batches L01 ÷ L04) increased, the obtained granules showed higher density and better tableting behavior - high hardness, low friability and good disintegration.

The optimal properties of the granules and tablets are achieved in batch № IAD L03. Replacement of povidone type K25 with povidone type K30 (batch № IAD L05) results in granules with higher mechanical strength but with a longer disintegration time.

The achieved optimal lubrication system is from the substance Glycerol dibehenate - batch № IAD L03, at a concentration of 3.08%.

Decrease in the concentration of Glycerol dibehenate - batch № IAD L08 or the use of magnesium stearate - batch № IAD L06 or its combination with stearic acid - batch № IAD L07 indicates the appearance of defects in the tablets - breakage, capping the top of the tablet as a result of insufficient lubrication of punches and dies.

The disintegration time is not significantly affected in the different batches as the content of the disintegrant wheat starch that is the same in all batches.

According to the Guideline on the investigation of bioequivalence, the pH dissolution profile of the active substance must be determined. The active substance is considered to be very soluble if the highest dose administered as an immediate release form is completely dissolved in 250 ml of buffers with a pH range of 1 to 6.8 at 37 ± 1 °C.

The solubility of Inosine acedoben dimepranol in the study media is shown in Table 7:

The data show that the substance IAD is practically insoluble in acidic media. However, it meets the criterion D: S < 250 ml in media with a pH range of 4.5 ÷ 6.8 at a temperature of 37 °C.

According to the pharmacopoeia, a volume of solvent medium of 900 ml is normally specified for tablets. At a maximum dose of 1000 mg IAD, the concentration of IAD in the solution will be 1.1 mg /ml, which is many times lower than the concentration of saturated IAD solution. Therefore, in media with a pH range of 4.5 ÷ 6.8 at a temperature of 37 °C, the „*Sink*" conditions will be met.

Table 7. Solubility results of IAD in the proposed dissolution media.

Solvent-media, temperature	Approximate Solubility IAD (mg/ml)	Criterion: Ratio Dose 1000 mg (D) : Solubility(S) D:S < 250 ml (37 °C)
Buffer, pH = 1.2, 37 °C	Practically does not dissolve	> 250
Buffer, pH = 4.5, 37 °C	264.0	3.79
Buffer, pH = 6.8, 37 °C	276.0	3.62

Experiments were performed for dissolution profile with batch № IAD L03 under the following conditions: pH 1.2, 4.5, 6.8 and stirrer speeds 50 rpm and 75 rpm.

The results of the dissolution profiles of the tested tablets are presented in the following graphs (Figs 1, 2).

The following observations were made during the test:

pH 1.2

- At stirrer speed 50 rpm

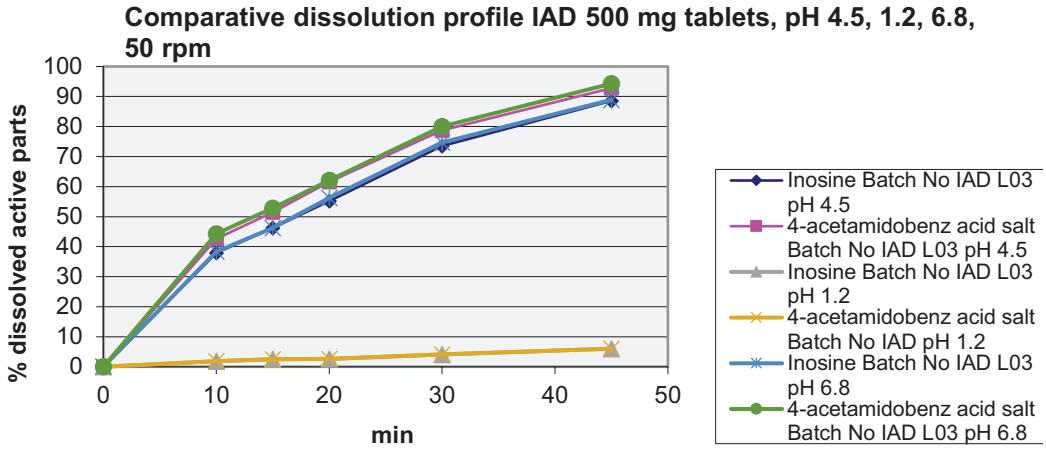

Figure 1. Comparative dissolution profile of IAD 500 mg tablets, batch № IAD L03, in medium with pH 1.2, 4.5, 6.8 (Ph Eur) and stirrer speed 50 rpm.

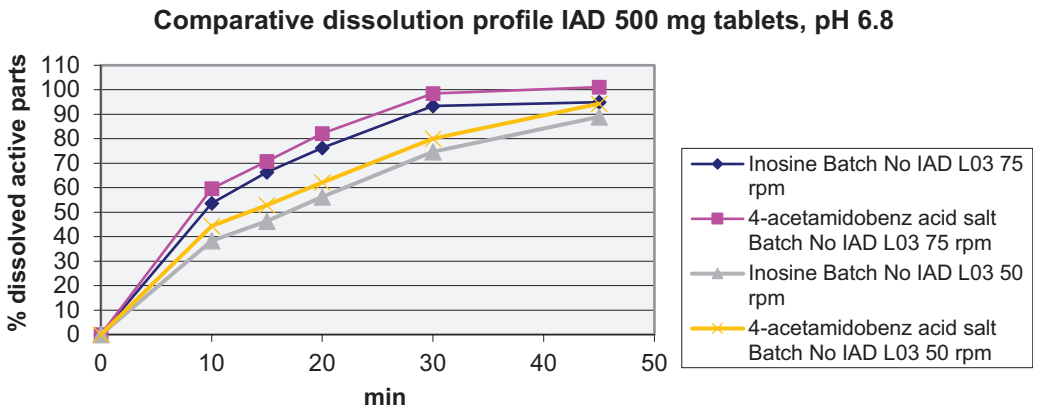

Figure 2. Comparative dissolution profile of IAD 500 mg tablets, batch № IAD L03, in medium with pH 6.8 (Ph Eur) and stirrer speed 50 rpm and 75 rpm.

The product is practically insoluble, large relative standard deviations.

pH 4.5

- At stirrer speed 50 rpm

Dissolution is delayed, large relative standard deviations. There is a "coning" effect.

pH 6.8

- At stirrer speed 50 rpm,

Dissolution is delayed, large relative standard deviations. There is a "coning" effect.

- At stirrer speed 75 rpm.

Complete dissolution, small relative standard deviations - less than 10%.

According to the test conditions, 75 rpm and phosphate buffer pH 6.8 are the most suitable stirrer speed and dissolution media for IAD 500 mg tablets.

In addition, a dissolution profile test was performed under the established conditions - pH 6.8 and stirrer speed 75 rpm and the market product Isoprinosine 500 mg tablets (batch № 1980065, expiration date 02/2024), in order to assess the similarity of the profile to that of IAD 500 mg tablets, batch № IAD L03.

The results are presented in Fig. 3.

The dissolution profiles of both products show similar behavior and are characterized as similarly rapid - 85% of the active substance is released within 30 minutes.

To demonstrate the similarity of dissolution profiles according to the Guideline on the investigation of bioequivalence, the value of the similarity factor f_2 is calculated:

$$f_{2\ \text{inosine}} = 72.59 \text{ and}$$
$$f_{2\ \text{4- acetamidobenzoic acid salt}} = 74.34$$

According to criterion f_2, values between 50 and 100 indicate the similarity of the dissolution profiles of the two products.

The discriminant power of the dissolution method was tested in an experimental batch in which the binder povidone was added twice as high as an amount. In this case, it is assumed that the binding forces (cohesion) in the tablet will be increased, which will lead to a delay in the disintegration time and respectively a delay in the dissolution time. This behavior will be reflected in the specified dissolution rate parameter.

The data obtained from the study are the following:

- The dissolution rate for 30 minutes of Inosine is 74% and of 4-acetamido benzoic acid salt is 79%. The obtained values do not meet the specified norms - 85% of the active substance is released within 30 minutes.
- The process of dissolution of the tablet is slow due to the increase in the amount of binder.
- The chosen dissolution method allows discrimination of batches with different *in vitro* release characteristics.

Batch № IAD L03 500 mg tablets was packed in a blister consisting of PVC /PVdC film (250 μm /40 g /m^2), thermally sealed with aluminum foil (20 μm) and stability tests were performed under accelerated conditions - 40 °C /75% RH for six months according to Note for guidance on stability testing.

The analytical results are presented in Table 8:

The results of the batch impurity profile after 6 months of storage under accelerated conditions did not show any significant change.

No changes in the physicochemical parameters of the tablets were observed.

The results correspond to the product specification.

Conclusion

Based on the results of the study, an optimal composition and process for the production of IAD 500 mg tablets with immediate release of the active substance is proposed.

The tablets are prepared by wet granulation process with povidone 25, which is included in the inner part of the granules.

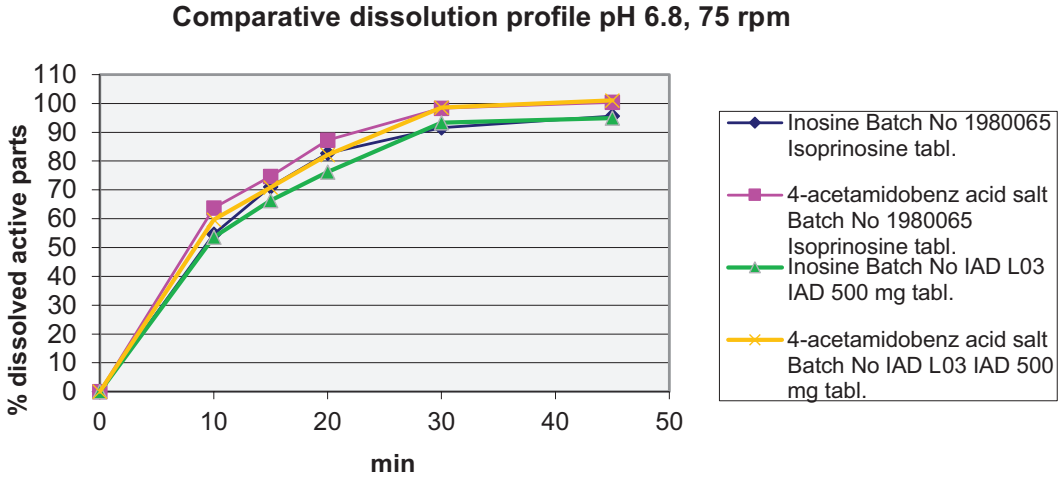

Figure 3. Comparative dissolution profile of Isoprinosine 500 mg tablets, batch № 1980065 and IAD 500 mg tablets, batch № IAD L03.

Table 8. Stability study batch № IAD L03 500 mg tablets.

Test	Specification	Initial analysis	Testing after 3 months	Testing after 6 months
1. Appearance	White to off-white, round, flat tablets, diameter 13 mm	Complies	Complies	Complies
2. Identification Inosine Acedoben Dimepranol - UV absorption - HPLC	Compliance with the tests	Meets the tests	Meets the tests	Meets the tests
3. Average mass, mg /tablet and uniformity of mass, mg	From 617.5 to682.5 (650 ± 5%)	650.4 Complies	650.6 Complies	650.7 Complies
4. Disintegration, min	No more than 15	7.0	7.0	7.5
5. Dissolution, %, within 30 min:				
Inosine	Not less than 80 (Q=75)	93	92	90
4-acetamido benzoic acid salt	Not less than 80 (Q=75)	97	95	93
6. Impurities, HLPC:				
6.1 Hypoxanthine, %	Not more than 0.2	n.d.	0.01	0.02
6.2 4-aminobenzoic acid, %	Not more than 0.2	0.05	0.07	0.10
6.3 Each unspecified impurity, %	Not more than 0.1	n.d.	< LOQ	< LOQ
6.4 Total impurities, %	Not more than 0.5	0.05	0.08	0.12
7. Content of IAD, HPLC, mg/tabl				
Inosine (theoretically 24.05%)	120.25 (95.0 – 105.0%)	124.30	121.26	118.94
4-acetamido benzoic acid salt (theoretically 75.95%)	379.75 (95.0 – 105.0%)	373.55	374.68	369.34
Sum of active components	500.00 (95.0 – 105.0%)	497.85	495.94	488.28

The study shows that the substance IAD is practically insoluble in acidic media. However, it meets the criterion D: S < 250 ml in media with a pH range of 4.5 ÷ 6.8 at a temperature of 37 °C.

A method for testing the dissolution of tablets has been developed and the following conditions have been established: apparatus, stirrer speed and type of medium.

A liquid chromatographic method for determining the content of IAD has been developed.

The similarity of the active substance release profiles between the test product – IAD 500 mg tablets and the reference product – Isoprinosine 500 mg tablets has been demonstrated.

The results of the stability study indicate that the tablets remain stable under the conditions of observation.

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