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Research Article

Effect of binder type on physical and in vitro properties of high dose inosine acedoben dimepranol tablets

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Abstract

The present work was conducted with the aim to formulate and evaluate the immediate release of 1000 mg tablets containing Inosine Acedoben Dimepranol (IAD). All the samples of the tablets containing 1000 mg IAD were prepared by conventional wet granulation method. Various type of binders like povidone, wheat starch, pregelatinized starch (starch 1500™ , Colorcon), microcrystalline cellulose and macrogol 6000 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 № IAD1000 L04 was found to be the best for producing IAD 1000 mg tablets. The optimal lubricant system is glycerol dibehenate at a concentration of 2.94% plus magnesium stearate at a concentration of 0.46%. Optimized formulation was evaluated for *in-vitro* dissolution test. Stability studies were performed for the selected composition.

Keywords

Inosine Acedoben Dimepranol, Inosine pranobex, 1000 mg tablets, binders, dissolution

Introduction

The active substance Inosine Acedoben Dimepranol (INN) (IAD), also known as Inosine pranobex and Methisoprinol has been proven to positively impact the host's immune system, by enhancing T-cell lymphocyte proliferation and activity of natural killer cells, increasing levels of proinflammatory cytokines, and thereby restoring deficient responses in immunosuppressed patients. At the same time, it has been shown that it can affect viral RNA levels and hence inhibit growth of several viruses. Due to its immunomodulatory and antiviral properties as well as its safety profile, it has been widely used against viral infections and diseases among which subacute sclerosis panencephalitis, herpes simplex virus, human papilloma virus, human immunodeficiency virus, influenza and acute respiratory infections (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) for the treatment of viral infections.

According to the Summary of product characteristics of the product Isoprinosine™ 500 mg tablets (Bulgarian drug agency 2022), the dosage is as follows: for adults and elderly patients, the recommended daily dose is 50 mg/kg of body weight (1 tablet per 10 kg), usually 3 g/day to no more than 4 g inosine acedoben dimepranol daily, administered orally in 3–4 equally divided doses during the day.

Due to its potent immunomodulatory properties, IAD has been intensively evaluated for its potential as a COVID-19 medication (Beran et al. 2021). For the treatment of COVID-19 it is recommended to use the maximum dosage of 4×2 tabl. (4×1000 mg = 4 g/ day).

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 P 1974):

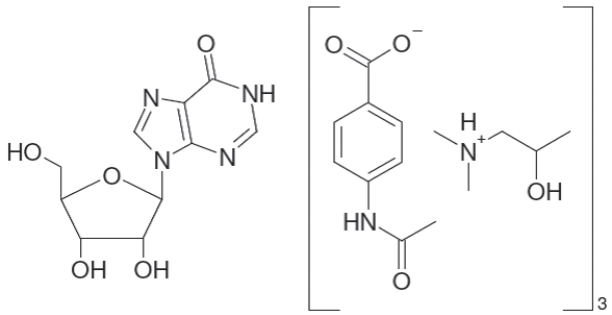

Figure 1. The active ingredient is not included in any pharmacopoeia.

In the first publication (Kafedjiiski K 2022) it is concluded: „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" (p. 324).

Since in most indications of IAD 500 mg tablet a single dose of 1000 mg is prescribed, the development of 1000 mg tablet is undertaken, which is more convenient for the patient. The shape of the tablet should be oblong, which makes it easier for the patient to swallow it. In the pharmaceutical practice, there are a number of examples of popular active substances with a dose of 1000 mg or more in the form of tablets, such as paracetamol, piracetam, metformin, etc.

The 1000 mg dose of the as the dosage form Isoprinosine powder for oral solution in a sachet was introduced on the market in Bulgaria in 2020. Children and adults who have trouble swallowing tablets or capsules may find powders for oral solution more acceptable. Dissolution rate of oral powders containing water-soluble drugs is generally faster than tablets or capsules, in which disintegration of the tablet or the capsule shell is required prior to dissolution. A disadvantage of powder forms is that they are bulky and inconvenient to be carried. A glass of water and a spoon are needed to dissolve the product before administration. Masking the unpleasant taste of the active substance can be a problem with this type of dosage form. The data of IMS Bulgaria for the annual sales in 2021 of Isoprinosine products are as follows: tablets 500 mg × 50 – 172 413 packages (5 849 313 BGN), powder for oral solution × 24 – 5 008 packages (183 472 BGN). Therefore, the share of tablets in sales is about 97% and it is the most preferred form by patients.

Tablets 1000 mg IAD have already been registered in Poland under the trade name Neosine forte - Aflofarm Farmacja Polska Sp. z o.o. in 2019. The dosage is the same: the recommended dose is 50 mg/kg body weight daily (usually 1000 mg, i.e. 1 tablet administered 3 to 4 times a day). The maximum dose is 4.000 mg daily.

In the Summary of product characteristics of Neosine forte tablets, the following excipients are described: wheat starch, mannitol, povidone and magnesium stearate. The literature review shows there are no articles on the pharmaceutical development of IAD tablets.

The approach to develop a higher dose of a solid dosage form i.e. tablets in pharmaceutical and regulatory practice is usually based on the principle of proportionality. Preliminary experiments have shown this principle is not fully applicable in the case of the IAD substance.

On the other hand, in the development of a 500 mg tablet, the solvent ethanol 96%: water = 1: 1 for granulation is used, and in industry only water is preferred as a solvent due to ecological and explosiveness related concerns

Therefore, the aim of this work is to evaluate and compare the effect of some commonly used binders and develop a 1000 mg IAD tablet with immediate release of the active substance by using only water solvent for the granulation process.

Materials and methods

Materials

Inosine Acedoben Dimepranol (ABC Farmaceutici S.p.A., Italy), wheat starch (Roquette), povidone K25 (Kollidon 25, 30 BTC Europe GmbH/ BASF), pregelatinized starch (starch 1500, Colorcon), Macrogol 6000 (Clariant), microcrystalline cellulose PH 102 (Vivapur JRS Pharma), 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 Table 1.

The size of the laboratory batches is 1 000 tablets (1292 g).

The wet granulation method is used for the production of all batches.

The ingredients are measured according to the recipe and sieved through a sieve with a pore size of 1.25 mm.

Preparation of inosine acedoben dimepranol granules

Inosine acedoben dimepranol and binders are loaded into the planetary lab mixer. The mass is mixed dry for 5 minutes. The resulting dry mass is moistened with the solvent or binder solution according to the recipe of the batch. The

Table 1. Compositions of laboratory batches.

Ingredients mg/tabl	Batch №											
	IF L01	% w/w	IF L02	% w/w	IF L03	% w/w	IF L04	% w/w	IF L05	% w/w	IF L06	% w/w
Granules												
Inosine Acedoben Dimepranol	1000.0	77.40	1000.0	77.40	1000.0	77.40	1000.0	77.40	1000.0	77.40	1000.0	77.40
Wheat starch	120.0	9.29	116.0	8.98	–	–	116.0	8.98	–	–	116.0	8.98
Kollidon K25	50.0	3.87	50.0	3.87	50.0	3.87	50.0	3.87	–	–	–	–
Starch 1500	–	–	–	–	116.0	8.98	–	–	166.0	12.85	–	–
Macrogol 6000	–	–	–	–	–	–	–	–	–	–	50.0	3.87
Water purified*	45.0		45.0		45.0		45.0		60.0		50.0	
Mixture for tableting												
Granules IAD	1166.0		1166.0		1166.0		1166.0		1166.0		1166.0	
Microcrystalline cellulose PH 102	–	–	–	–	–	–	34.0	2.63	34.0	2.63	34.0	2.63
Mannitol 200 SD	34.0	2.63	34.0	2.63	34.0	2.63	–	–	–	–	–	–
Wheat starch	48.0	3.72	48.0	3.72	–	–	48.0	3.72	–	–	48.0	3.72
Starch 1500	–	–	–	–	48.0	3.72	–	–	48.0	3.72	–	–
Glycerol dibehenate	40.0	3.10	38.0	2.94	38.0	2.94	38.0	2.94	38.0	2.94	38.0	2.94
Magnesium stearate	–	–	6.0	0.46	6.0	0.46	6.0	0.46	6.0	0.46	6.0	0.46
Total	1292.0	100.0	1292.0	100.0	1292.0	100.0	1292.0	100.0	1292.0	100.0	1292.0	100.0

* The solvent evaporates during the production process

solvent or solution is then added to the mixture over 5 minutes. Finally, it continues to be mixed for another 5 min.

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 1.25 mm sieve.

Preparation of a mixture for tableting

Excipients of the external phase are added to the obtained granules and homogenized in a diffusion mixer for 15 min. Lubricants are added and homogenized for 5 min.

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: oblong with dimensions: 21.5 x 8.2 mm;

Average mass per tablet 1292 mg ± 5.0% (1227.4–1356.6);

Hardness: target value 80 N (from 60 N to 130 N);

Friability: not more than 1.0%.

Characterization of the finished granules

The granules are evaluated by the "Hausner ratio" 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

A liquid chromatographic method is used as described in the first article (Kafedjiiski K 2022).

The total content (X) in mg/tabl 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-acetamidobenzoic acid salt, mg/tablet.

Dissolution testing

The already established conditions and procedure for testing the dose of IAD 500 mg tablets were used (Kafedjiiski K 2022). The dissolution rate of IAD from tablets was studied in 900 ml of dissolving medium with temperature set to37 ± 0.5 ^{0}C using Ph. Eur. Dissolution Test Apparatus (Model Pharma Test PTWS-MA) with paddle stirrers.

Test time - 45 min.

Samples of 5 ml were taken after 10, 15, 20, 30 and 45 min from each vessel of the apparatus, filtered through a 0.45 μm filter and analyzed in a liquid chromatograph for the released amount of IAD such as Inosine and 4-acetamidobenzoic acid salt, in %.

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

Evaluation of the results: The amount of IAD released such as Inosine and 4-acetamido benzoicacid 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 the 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 the 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 this developed product. Other reasons behind are as follows:

- 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 of quality tablets.

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

Purified water was used as the granulation fluid to form the wetted mass of all formulations except IF L06, in which an aqueous solution of macrogol 6000 was used. The results of the tested physicochemical parameters of the batches are presented in Table 2.

Table 2. Results of tested physicochemical parameters.

Tested parameters	Evaluation					
	IF L01	IF L02	IF L03	IF L04	IF L05	IF L06
Bulk density of granules, g/ml	0.500	0.476	0.488	0.476	0.500	0.500
Tapped density, g/ml	0.541	0.556	0.541	0.526	0.500	0.526
Hausner ratio of granules	1.081	1.167	1.108	1.105	1.000	1.053
Residual moisture of granules, %	2.8	2.4	2.6	2.2	2.9	2.7
Average mass per tablet (mg)	1293.2	1295.4	1293.8	1294.2	1294.6	1293.4
Hardness (N) n = 10; ± SD	60 ± 5.5	65 ± 6.4	75 ± 5.6	96 ± 6.8	55 ± 7.6	45 ± 7.2
Disintegration (min)	10.0	10.0	11.0	10.0	12.0	9.0
Friability (%)	0.68	0.62	0.58	0.51	0.84	0.73
Defects in the appearance of the tablets, %	3.0	no	no	no	no	1.0

With regards to the „flow" property of the granules, the „Hausner ratio" data showed all batches have good criterion values < 1.25.

The composition of batch IF L01 is almost twice proportional to the established composition of IAD 500 mg tablets (Kafedjiiski K, 2022), with minimal reduction of some excipients accordingly thus to achieve an appropriate total mass for the selected oblong punch. The data from the tested characteristics of the obtained tablets show that the tableting process produces tablets with defects and low hardness. With the inclusion of an additional lubricant such as magnesium stearate in the next composition IF L02, the tableting process is thus improved and the defects disappear, but the low hardness is maintained. In order to strengthen the cohesion forces in the tablet, microcrystalline cellulose is included in the external phase - composition IF L04. The resulting tablets are characterized by the desired optimal properties - high hardness, low friability and also disintegration time within 10 min.

In the composition IF L03, wheat starch was replaced by starch 1500™. This is a starch that has been previously gelatinized and dried to powder form. Partially pregelatinized starches have a mixture of properties of both native and fully gelatinized starches. This makes them useful as both a binder and a disintegrant in wet granulated formulations. Starch 1500 can be added directly to the granulator bowl and water can be utilized to granulate. The results show there is no significant change in the properties of the tablets.

The composition IF L05 was prepared according to the instructions of Colorcon for the application of starch 1500 to water-soluble active substances (Colorcon Technical Literature 2019). In this case for granulation, it is used only starch 1500 as a binder and in the outer phase is added microcrystalline cellulose. However, there is no improvement in the properties of the tablets as low hardness and longer disintegration time are achieved.

In the composition IF L06, another wet granulation binder is being experimented with macrogol 6000, which is typically used for water-soluble active substances. In solid dosage formulations, higher molecular weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity of granules. The use of polyethylene glycols is proposed, since it has been verified that the same when in solution, act not only as binder in the granulation process, but also effectively contributes to the increase of density of the granules, reducing the volume originally occupied by the active principles (Rowe et al. 2009). The results show that in the case of the active substance IAD, macrogol 6000 is a weak binder, although it is applied in the form of a solution. The resulting tablets have low hardness.

From the evaluation of the results, the following effects of binders are observed:

- The strongest and most suitable binder for the granules is povidone in combination with wheat starch, as also was found for the dose of 500 mg tablets. Wheat starch can be replaced by pregelatinized starch, but it is much more expensive and economically not justified.
- Using only water as a binder solvent does not affect the properties of the resulting granules.
- The inclusion of microcrystalline cellulose in the external phase of the composition further strengthens the binding properties and allows obtaining 1000 mg tablets with the desired properties.
- The use of mannitol as a binder in the external phase of the composition is not effective for the 1000 mg dose.

Dissolution tests were performed according to the guidelines of Ph Eur "Recommendation on dissolution

testing" and the monograph "Dissolution test for solid dosage forms", as well as the EMA 2010 guidelines "Guideline on the investigation of bioequivalence" and "Reflection paper on dissolution specification for generic solid oral immediate release products with systemic action".

The established conditions and procedure for testing the dose of IAD 500 mg tablets were used.

According to the data for dissolution of IAD, "Sink" conditions are met for the dose of 1000 mg tablets in media with a pH range of 4.5 ÷ 6.8 at a temperature of 37 °C.

Experiments were performed for comparison of the dissolution profiles between IAD 1000 mg tablets, batch IF L04 and IAD 500 mg tablets, batch IAD L03, under the following conditions: dissolving media with pH 6.8 (phosphate buffer), 4.5 (acetate buffer) and stirrer speed set to 75 rpm to assess the similarity of the dissolution profiles of the two doses of IAD tablets. The results of the dissolution profiles of the tested tablets are presented in the following graphs (Figs 2, 3).

The dissolution test was also carried out with sample IF L03 in order to evaluate the effect of the binder pregelatinized starch (Fig. 4).

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

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:

$$f_{2\ \text{inosine}} = 79.19 \text{ and}$$
$$f_{2\ 4\text{ - acetamidobenzoic acid salt}} = 80.66$$

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

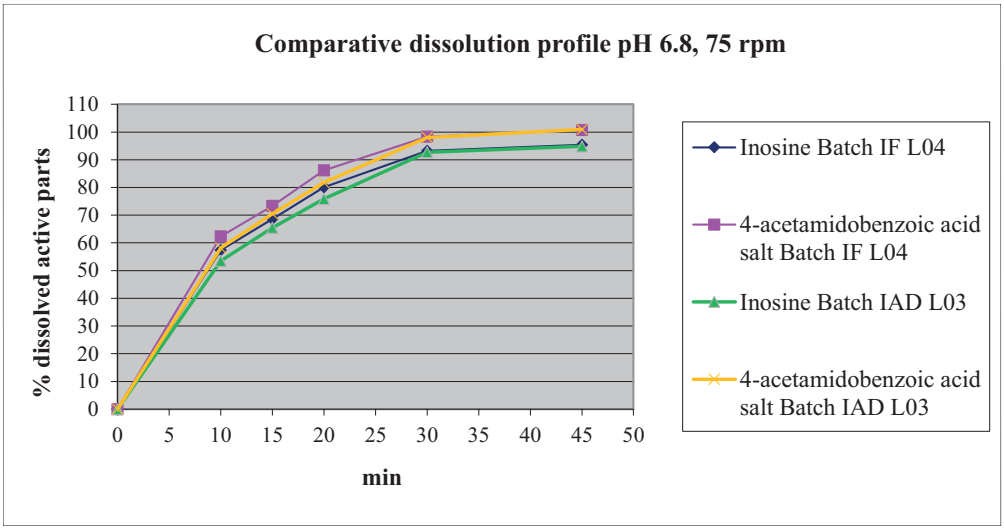

Figure 2. Comparative dissolution profile of IAD 1000 mg tablets, batch IF L04 and IAD 500 mg tablets, batch IAD L03, pH 6.8, expressed by the contents of the active components Inosine and 4-acetamidobenzoic acid.

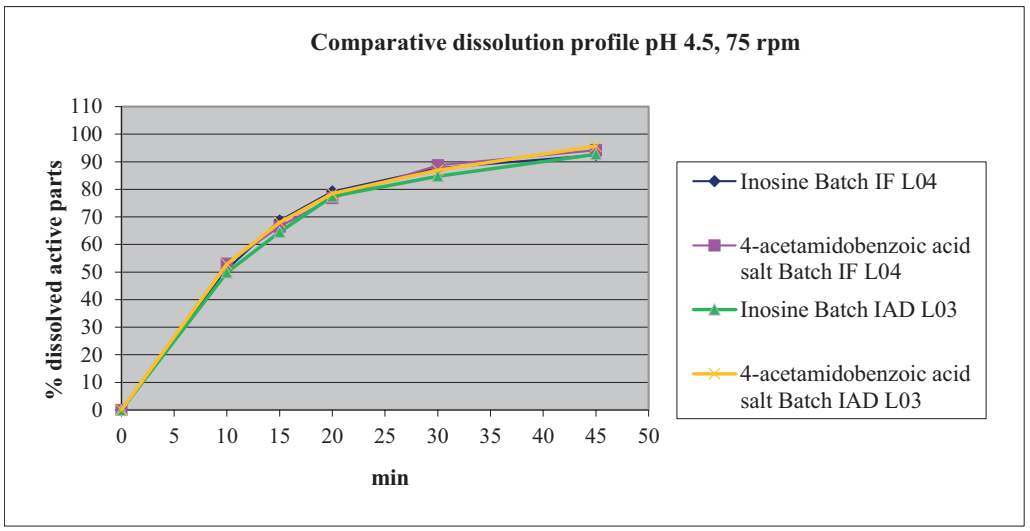

Figure 3. Comparative dissolution profile of IAD 1000 mg tablets, batch IF L04 and IAD 500 mg tablets, batch IAD L03, pH 4.5, expressed by the contents of the active components Inosine and 4-acetamidobenzoic acid.

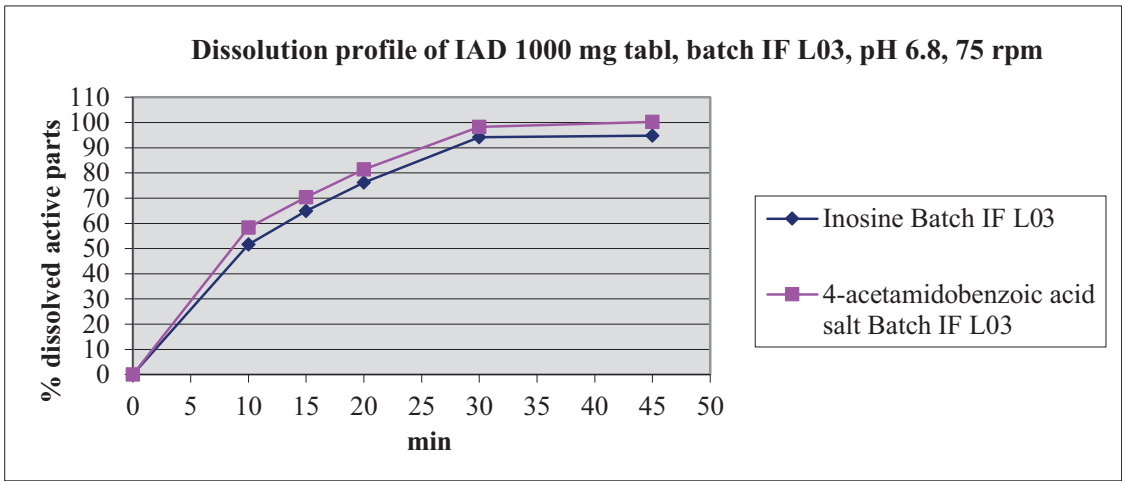

Figure 4. Dissolution profile of IAD 1000 mg tablets, batch IF L03, pH 6.8, expressed by the contents of the active components Inosine and 4-acetamidobenzoic acid.

Table 3. Stability study tablet batch № IF L04.

Test	Specification	Initial analysis	Testing after 3 months	Testing after 6 months
1. Appearance	White to off-white, oblong, biconvex tablets with a slight ammonia odor	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 1227.4 to 1356.6 (1292 ± 5%)	1294.2 Complies	1294.6 Complies	1294.8 Complies
4. Disintegration, min	Not more than 15	10.0	10.0	10.0
5. Dissolution, %, within 30 min: Inosine 4-acetamidobenzoic acid salt	Not less than 80 (Q=75) Not less than 80 (Q=75)	93 98	92 96	90 95
6. Impurities, HLPC:				
6.1 Hypoxanthine, %	Not more than 0.2	n.d.	n.d.	0.02
6.2 4-aminobenzoic acid salt, %	Not more than 0.2	0.05	0.06	0.09
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	0.06	0.11
7. Content of IAD, HPLC, mg/tabl Inosine (theoretically 24.05%) 4-acetamidobenzoic acid salt (theoretically 75.95%) Sum of active components	240.50 (95.0–105.0%) 759.50 (95.0–105.0%) 1000.00 (95.0–105.0%)	233.46 770.66 1004.12	233.04 770.22 1003.26	232.32 769.43 1001.75

The dissolution profiles of both products show similar behavior and are characterized by a certain delay in the release of the active substance compared to the medium at pH 6.8.

To demonstrate the similarity of dissolution profiles according to CPMP/EWP/QWP/1401/98 Rev. 1 /Corr **, the value of the similarity factor f_2 is calculated.

The result obtained is as follows:

$$f_{2\ \text{inosine}} = 76.47 \text{ and}$$
$$f_{2\ 4\text{ - acetamidobenzoic acid salt}} = 85.24$$

According to criterion f2 requirement, values between 50 and 100 indicate the similarity of the dissolution profiles of the two products.

The data show that in the medium with pH 1.2, the dissolved amount of IAD such as Inosine and 4-acetamidobenzoic acid salt is insignificant. The low values are due to the chemical nature of IAD, which complex is practically insoluble in this environment, rather than the influence of formulation factors on the dosage form. As the "Sink" conditions are not met for this environment, the similarity factor f2 is not calculated accordingly.

The dissolution profile of sample IF L03, in which wheat starch is replaced by the pregelatinized starch, is also characterized as rapid - 85% of the active substance is released within 30 min. Therefore, the Starch 1500™/Povidone binder combination favors the immediate release of IAD from the tablet matrix under the test conditions.

Tablet Batch IF L04 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 3.

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

Wet granulation technique can be successfully used to overcome the poor compression properties of Inosine Acedoben Dimepranol powder and also to produce high-dose 1000 mg tablets with immediate release of the active substance.

Wet granulation was tested with several binders - Wheat starch /Povidone; Starch 1500™/ Povidone, Starch 1500™ and Macrogol 6000.

The Wheat starch /Povidone and Starch 1500™/ Povidone mixtures, including microcrystalline cellulose in the outer phase were found to be the best for producing IAD 1000 mg tablets.

The optimal lubricant system is glycerol dibehenate / magnesium stearate.

A similarity of the dissolution profile of the 1000 mg IAD tablet dose versus the 500 mg IAD tablet dose was demonstrated.

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

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