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Regular Article

Research and Development the Prescription of Sofosbuvir Tablets

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Abstract: The prescription of sofosbuvir tablets was screened to select the best prescription proportions. Methods: According to the prescription technology of foreign listed tablets "sovaldi®", experiments of diluents, disintegrating agents, binders, lubricants and coating process were investigated, including the stability study of self-made samples and reference tablets under the conditions of high temperature, high humidity and illumination. We aimed to screen a reasonable prescription process. Results: Prescription process was ultimately determined including: sofosbuvir 400 mg, mannitol 360 mg, microcrystalline cellulose 360 mg, cross-linked sodium carboxymethyl cellulose 60 mg, magnesium stearate 14 mg, gum arabic 6 mg, opadry film coating powder 36 mg, and chose purified water as a binder. Conclusion: The determined prescription process was stable, and the production process was not harsh, it was suitable for scale-up production. The results of stability study and the dissolution behavior in vitro were similar to those of commercial products, so the prescription is design reasonably.

Keywords: sofosbuvir tablets, stability study, prescription technology, reference tablet "sovaldi ®".

1. Introduction

The molecular formula of sofosbuvir is $C_{22}H_{29}FN_3O_9P$, with a relative molecular mass of 529.453[1-2]. Sofosbuvir is a direct acting antiviral drug, which inhibits the hepatitis C virus RNA depend on RNA polymerase, NS5B gene. Sofosbuvir is effective in the treatment of 1, 2,

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3 genotypes or genotype 4 HCV subjects, including the hepatocellular carcinoma subjects who are waiting for liver transplantation and meet with the Milan standard, and the HCV/ HIV-1 co-infected patients.

The traditional standard treatment for HCV infection is interferon α or peg interferon α combined with ribavirin; the treatment program is expensive with large adverse drug reactions. When it was used for the treatment of genotype 2 and 3 HCV infections, the sustained virological response (SVR) is 80%, while the SVR for HCV infected individuals of genotype 1 is only about 50%[3]. In order to replace the currently used interferon injection therapy, global market for the treatment of chronic hepatitis C have appeared telaprevir, boceprevir, sofosbuvir one after one, the first two are HCV nonstructural protein 3/4A serine protease inhibitors, which are suitable for HCV infection of gene type 1, but need to be combined with peg interferon α and ribavirin [4].

Sofosbuvir, approved by FDA on December 6, 2013, is a new type of anti HCV drugs, which is suitable for various genotypes of hepatitis C treatment [5]. Clinical trials confirmed that the SVR of sofosbuvir combined with peg interferon α and ribavirin was up to 90% for genotype 1 and 4 HCV infections, for genotype 2 HCV infections, the SVR of sofosbuvir combined with ribavirin was 89%~95%, for genotype 3 HCV infections, the SVR of sofosbuvir combined with ribavirin for 24 weeks was 84%.

In order to increase the range of clinical medication selection and reduce the cost of medication for patients, the prescription process was screened and optimized by referring to GILEAD's sovaldi® in this study. The prescription of sofosbuvir tablets was determined, the main technical parameters were verified, and the quality standard of the product was established and realized the expected industrialized production.

Table 1. The Prescription of Sofosbuvir

Ingredients	Function
Sofosbuvir	active ingredient
cross-linked sodium carboxymethyl cellulose	disintegrant
purified water	binder
microcrystalline cellulose	diluent
mannitol	diluent
gum arabic	lubricant
magnesium stearate	lubricant
opadry	coating material

2. Experiment and Method

2.1 Instrument and Equipment

Hardness Tester, Dissolution Tester, Disintegration Tester, and Friabilator.

2.2 Prescription Composition

The active ingredient of this product was sofosbuvir, the dosage form of this product is film coated, it is used by oral, and the specification is 1.2 g, which contains 400 mg sofosbuvir in each tablet. The specific prescription and the function of each ingredient were shown in **Table 1**.

2.3 Prescription Screening

2.3.1 Selection of Diluents

According to the prescription technology of foreign listed tablets "sovaldi®", mannitol and microcrystalline cellulose were chosen as diluents, and the amount of the diluents were adjusted respectively. The appearance, hardness and crispness of tablets were taken as the main evaluation indexes to select the kinds of diluents and its amount. The detection method of brittleness means taking 10 pieces of this product, blow off the powder with a blower, then weigh it accurately. Rotate it in the cylinder for 100 times, remove the powder, weigh the powder accurately, and the weight loss must be not more than 1%. The calculation method is (weight before crushing - weight after crushing)/weight before crushing×100%. The measurement method of hardness was taking 10 pieces of this product in the hardness tester one by one, and measured the hardness of each piece, then calculated the average values of the 10 tablets. **Table 2** was the result of the selection of diluents.

Table 2. The Result of The Selection of Diluents.

No.	API(mg/tablet)	Microcrystalline cellulose (mg/tablet)	Mannitol (mg/tablet)	Appearance	Average hardness (N)	Friability (%)
1	400	0	720	smooth	115	0.68
2	400	720	0	rough, some spots	100	0.79
3	400	200	520	smooth	130	0.4
4	400	360	360	smooth	145	0.11
5	400	400	320	smooth	144	0.23

According to the test results, we knew the filling effect of the two diluents. No.1 and No.2 showed that if we only used microcrystalline cellulose or mannitol as diluent, the hardness of the tablet was not enough, besides, when the microcrystalline cellulose was used alone without mannitol, the surface of the tablets were rough with some spots. No.3 showed the appearance and hardness of the tablets were good, but the friability was larger for the large amount of mannitol. No.4 and No.5 not only had good appearance and hardness, but also had small friability. Considering that microcrystalline cellulose has strong water absorption, the disintegration performance is good. The larger amount of microcrystalline cellulose was used the harder to control the dissolution rate. Therefore, from the aspects of formability, preparation cost, performance of tablets, we finally choose No.4 as the basic prescription for further optimization.

2.3.2 Selection of Disintegrating Agent

Disintegrating agents are excipients that promote the disintegration of tablets in the stomach and intestine. The tablets were pressed under high pressure, the gap was small and the adhesion was strong, it was difficult to dissolve, so the disintegration agent was an important additive to ensure the dissolution and absorption of drugs in vivo. In order to ensure the effective dissolution, the disintegrating agent was screened.

Referring to the "sovaldi®", cross-linked sodium carboxymethyl cellulose was used as the disintegrating agent. Cross-linked sodium carboxymethyl cellulose is a common disintegrating agent for tablets, it is insoluble in water, but it can absorb water and swell. Also, it has a large water absorption capacity. The amount of cross-linked sodium carboxymethyl cellulose was screened by taking the appearance, disintegration time and dissolution curve of the tablets as evaluation indexes. The disintegration instrument was set with water temperature of 37°C, 6 pieces of tablets were placed in the basket, then started the disintegration instrument and recorded the disintegration time.

Table 3. The Results of The Amount of Cross-linked Sodium Carboxymethyl Cellulose

No.	Amount（mg/tablet）	Appearance	Disintegration Time（min）
6	6	ordinary smoothness	10
7	25	ordinary smoothness	6
8	50	Smooth	3
9	60	Smooth	1

The results showed that the prescription of No.6 used less amount of disintegrating agent, and the disintegration time was a little long. The disintegration time of No.7 was shorter than No.6, but the surface smoothness was ordinary. Both No.8 and No.9 had short disintegration time and smooth surface. Compared the dissolution curves of No.8 and No.9, and the results were shown in **Figure 1**.

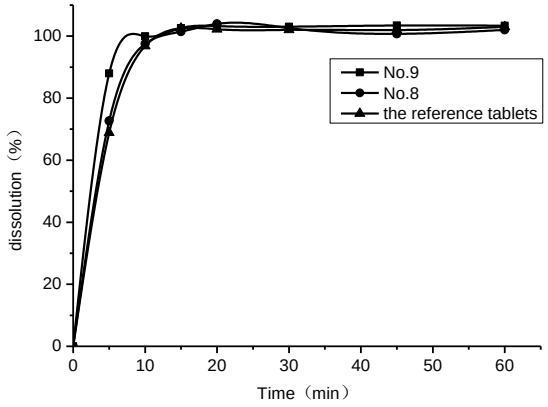

Figure 1: The Dissolution Curve of No.8, No.9 and the reference products

The results showed that products made by the prescription of No.9 dissolved quicker, and it dissolved completely in 10 min. The dissolution curve of No.8 was basically the same as that of the reference products. Therefore, the No.8 was determined, so the amount of cross-linked sodium carboxymethyl cellulose was selected at 60 mg/tablet.

2.3.3 Selection of Binding Agent

In order to ensure the formability, compressibility and liquidity of the particles, the types and the amount of binding agent were screened. The common binding agent for wet process is water, different proportion of ethanol solution, starch, povidone K30 and so on. In the sovaldi®'s prescription list, there was no starch and povidone K30. In order to ensure the safety of this product, we choose the same excipients as the sovaldi®, so we choose water and

Table 4. The Results of the selection of binding agent

No.	Type	Granules Properties	Angle of Repose	Appearance	The degree Difficulty of Sieving
10	water	suitable particles, good formability	33	smooth	easy
11	50% ethanol solution	suitable particles, good formability	35	smooth	easy

50% ethanol solution as the binding agent to investigate. The selection of binding agent was carried out with the degree of difficulty in granulation, particle formability, hardness and the appearance of tablets as evaluation indexes. The test results were shown in **Table 4**.

The results showed that both water and 50% ethanol solution as the binding agent can get good results. Considering that water is safer and cheaper than ethanol. Therefore, water was chosen as the binding agent.

2.3.4 Selection of Lubricants

The lubricant is added to reduce the friction between the tablet and the die wall, and to ensure the uniform pressure distribution during the pressing process. The most commonly lubricant used is magnesium stearate. The lubricants used in the "sovaldi®" tablet were magnesium stearate and gum arabic, so the amount of magnesium stearate and gum arabic were investigated. The appearance of tablets, production of tablets and the fluidity of particles were taken as evaluation indicators. The specific results are shown in **Table 5**.

The test results showed that the prescription of No.12 had smooth surface, but lack of glossiness. The surface of No.13 was out-of-flatness with some spots, and sticky punch when pressing production. The prescription of No.14 used magnesium stearate and gum arabic as its lubricant, the surface was smooth, but the glossiness was not enough, it also had a slight stick punch. Both No.15 and No.16 had a very good surface and not stick punch. By comparing the hardness of the tablets made by No.15 and No.16, the No.15 had a lower hardness. So we chose the prescription of No.16, which the lubricants were magnesium stearate and gum arabic, each of them was 16 mg/tablet and 4 mg/tablet, respectively.

Table 5. The Results of Selection of Lubricant

No.	Magnesium Stearate (mg/tablet)	Gum Arabic (mg/tablet)	Appearance	Production of Tablets	Angle of Repose
12	20	0	smooth, lack of glossiness	non stick punch	35°
13	0	20	not smooth, some spots	stick punch	34°
14	19	1	smooth, low glossiness	slight stick punch	31°
15	18	2	smooth	non stick punch	29°
16	16	4	smooth	non stick punch	28°

2.3.5 Selection of Coating Technology

In order to cover the bitterness of the active ingredient and avoid light, film coating is needed for the tablets. This product was intended to use a stomach-soluble film coating agent. And the coating process was as follows.

1) Preparation of opadry coating premixed solution with a concentration of about 12%.

Take the water as the solvent, and add the water to the agitator. Turn on the beater to make the whole liquid level form vortex, and then add the opadry film coating powder in a balanced speed. After charging, slow down the stirring speed until the liquid vortex had just disappeared. Continue stirring for 45min until the coating powder was completely dissolved. Turn off the beater, and filter the coating premixed solution through 80 mesh sieve, and collect the filtrate.

2) Coating process

Take the plain tablet, weigh it after sifting the fine powder. Then put it into the preheated coating pot. Turn on the coating machine, set the inlet temperature at 55~65 °C, set the rotation speed at 9 r/min, set the bed temperature at 35~40°C, set the pressure difference between -300~-500 Pa. When the coating layer was compact, the thickness was uniform, the tablets were dry, the coating weight was up about 2%~3%, the coating process can be finished.

The film coating tablets obtained by this prescription had smooth surface and good toughness. The dissolution curves of the samples after coating were investigated and compared with those of the reference tablets. The results were shown in **Figure 2**.

The results of the dissolution test showed that the f2=88.39 > 50, which means the self -made tablets were similar to the reference tablets in vitro.

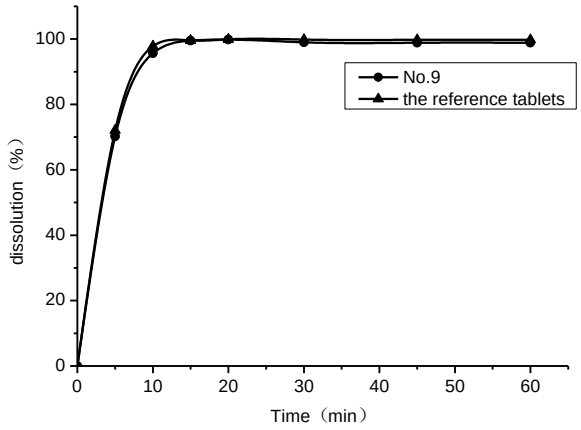

Figure 2: Dissolution curves of self-made and reference tablets

2.4 Investigation of Reproducibility and Stability

The enlargement of laboratory scale was based on the preliminary prescriptions and technology. Three batches were continuously enlarged with batch numbers of 20161101, 20161102 and 20161103, and per batch had 3000 pieces. On the one hand, the reproducibility of the technology was investigated; on the other hand, the influence factors were studied, including the stability of the product under the conditions of high temperature, high humidity and light.

Table 6. Quality Contrast Results

Batch Number	Character	Water（%）	Dissolution（%）	Labeled content（%）
20161101	film coating, white after removing coating	3.21	98.81	98.79
20161102	film coating, white after removing coating	3.18	98.02	98.91
20161103	film coating, white after removing coating	3.27	97.86	98.56
reference tablets	film coating, white after removing coating	3.23	98.97	99.02

Table 7. The Influence Factors Results of Batch No.20161101

Items	Requirements	Test Condition	Light（4500±500）Lx		High Temperature (60℃)		High Humidity（90±5）%RH	
		0d	5d	10d	5d	10d	5d	10d
character	film coating,white after removing coating	film coating,white after removing coating	film coating, white after removing coating	film coating, white after removing coating	film coating,white after removing coating	film coating,white after removing coating	film coating, white after removing coating	film coating,white after removing coating
Dissolution (%)	Not less than 80% in 30min	99.03	99.13	99.07	98.96	98.98	99.01	98.99
labeled content (%)	90.0～110.0%	98.79	98.77	98.82	98.77	98.78	98.8	98.81
absorption of moisture (%)	/	/	/	/	/	/	3.42	3.45

According to the quality standard draft requirements of sofosbuvir tablet, we tested the samples of batch No. 20161101, 20161102 and 20161103. We also compared them with the reference tablets in terms of character, dissolution and labeled content. The results were shown in **Table 6**.

From the above results, we knew that the items including characters, dissolution and labeled content of self-made product were similar to the reference tablets, which showed that these two products had the similar quality.

Placed the self-made samples (batch number: 20161101) and reference tablets in the conditions of high temperature of 60°C, relative humidity of (90±5)% and illumination of (4500±500) Lx for 10 days. Take samples to detect at the 5th day and the 10th day. According to the quality standard of this product, the key items of the character, labeled content, water and dissolution were investigated, and compared with the 0th day. The results were shown in **Table 7** and **Table 8**.

Table 8. The Influence Factors Results of The Reference Tablets

Items	Requirements	Test Condition	Light（4500±500）Lx		High Temperature (60^{O}C)		High Humidity （90±5）%RH	
		0d	5d	10d	5d	10d	5d	10d
character	film coating, white after removing coating	film coating, white after removing g coating	film coating, white after removing g coating	film coating, white after removing g coating	film coating, white after removing g coating	film coating, white after removing g coating	film coating, white after removing g coating	film coating, white after removing g coating
dissolution (%)	Not less than 80% in 30min	99.03	99.13	99.07	98.96	98.98	99.01	98.99
labeled content(%)	90.0～110.0%	98.79	98.77	98.82	98.77	98.78	98.8	98.81
absorption of moisture (%)	/	/	/	/	/	/	3.42	3.45

3. Results and Discussion

The comparative study on the influence factors of this product and the reference tablets for 10 days showed that, compared with the 0th day, there were no significant changes after 10 days under the condition of illumination of (4500±500) Lx and high temperature of 60°C,

while the product had moisture absorption under the condition of high humidity. In order to ensure the quality of the product, this product should be sealed and kept in the dry place.

Comparing the influence factors results between self-made products and the reference products showed that the trend of the change was similar. This showed that the sensitivity of the self-made products and the reference products was similar under the high temperature, high humidity and light conditions. It means the stability of self-made products was similar to that of the reference products.

The enlargement of laboratory scale was based on the preliminary prescriptions and preparation process, the sample had good appearance, good weight difference. The process was stable and not harsh. So it was suitable for enlarging production. At the same time, according to the influence factors results, the self-made products were similar to the reference products in character, dissolution behavior in vitro and the stability. It means the prescription of the self-made products was reasonable.

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