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FORMULATION AND *IN VITRO* EVALUATION OF PIDOTIMOD DISPERSIBLE TABLETS

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ABSTRACT: The aim of this article was to develop pidotimod dispersible tablet and optimize the ingredients for the tablets. The effect of ingredients (diluents, disintegrants and lubricants) on the characteristics of the tablets was evaluated. The pidotimod dispersible tablets were prepared by wet granulation. The effect of diluents on the tablets was investigated by Carr's index, dissolution, hardness, friability and taste. The effect of disintegrants on the tablets was determined by dissolution and cost. And the effect of lubricants on the tablets was studied by weight, hardness and dissolution behavior. The results showed that the optimum proportion was 400mg pidotimod, 120mg MCC, 80mg mannitol, 120mg CMS-Na, 60mg lactose, 20mg aspartame, 10mg magnesium stearate and 6%PVP 50% ethanol solution. Pidotimod dispersible tablets with optimum proportion showed acceptable taste, hardness, friability, dissolution behavior. The preparation process was simple and the tablets could be prepared by ordinary tablet production equipment. So it is suitable for mass industrialized production. The final tableting formulation and the simplified process both had tremendous potentials in commercial large-scale production.

INTRODUCTION: Pidotimod (Polymod, also known as Pidotimod) is a synthetic dipeptide, which acts as a biological response modifier (BRM) ¹.

It is capable of stimulating humoral and cellular immunity ², activate natural killer cell, enhance the phagocytic function of macrophage and neutrophilic granulocyte, promote the proliferation of lymphocyte induced by mitogens, and increase the production of cytokines such as Interleukin 2 and γ -interferon ^{3,4,5}.

In vitro studies for both human and animal specimens have indicated a good activity on innate and adaptive immune responses and have been documented by *in vivo* studies. These activities have been applied in clinical studies demonstrating the efficacy of pidotimod in reducing the rate of recurrent infections of the upper respiratory and urinary tracts in children.

The same results were obtained in recurrent respiratory tract infections in adults. Interestingly, these effects are more evident in the setting of immune defects such as senescence, downs syndrome, and cancer. Researches have also demonstrated that pidotimod itself does not have antibacterial activity, but when combined with antibacterial agents, pidotimod can be effective in improving clinical effects, promoting recovery, and shortening therapy time ^{6,7,8}.

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Oral administration is the most preferred route with the virtues such as ease of ingestion, avoidance of pain, patient compliance. Efforts to ease administration and enhance acceptability of the tablet to pediatric and geriatric patients triggered the development of a new formulation-dispersible tablet⁹.

British Pharmacopoeia defined dispersible tablets (DPTs) as the film-coated or uncoated tablets intended to be dispersed in water before administration giving a homogeneous dispersion¹⁰. There are two types of dispersible tablets which should be distinguished: one disintegrates quickly in the mouth without the need of water^{11, 12}, the other is dispersed in water to form a dispersion that is easy to use by pediatric and geriatric patients¹³. Up to now, there are various types of dispersible dosage forms that have been marketed by pharmaceutical companies, such as Afeksin® by Actavis Ltd., Coartem® by Novartis and Medicines, Amotaks® by Polfa Tarchomin SA^{14, 15}.

Because the ordinary pidotimod tablets are too big in shape to be taken by pediatric and geriatric. It is necessary to make a new preparation of pidotimod to take it conveniently. The aim of this study was to design a new formulation of pidotimod, pidotimod dispersible tablet, which dissolved in water quickly and could be swallowed by patients easily, and to determine the optimum formula. The pidotimod dispersible tablets were prepared by wet granulation. We investigated the effect of the ratio of MCC, lactose and mannitol in the tablets on physical properties and dissolution test. Types of lubricant were also investigated. So were the ratio and type of disintegrants in tablets.

MATERIALS AND METHODS: Pidotimod was obtained from Xianju Pharmaceutical Co.Ltd...(Zhejiang, China). Microcrystalline cellulose (MCC) was obtained from Huzhou Zhanwang Co. (Huzhou, China), Lactose, providone (PVP), crospovidone (PVPP), Carboxymethyl starch Sodium (CMS-Na) were obtained from ShanHe Excipients Co.Ltd (Anhui, China). Mannitol was obtained from Hua Xu Pharmaceutical Co.Ltd (Hebei, China). Magnesium stearate and talc were obtained from Ao Da Pharmaceutical Co.Ltd (Liaoning, China).

Preparation of the tablets: The pidotimod dispersible tablets were prepared by wet granulation. Pidotimod and excipients for tablets were weighed. All ingredients, except the lubricant, passed through 80 meshes and then were added and blended for 10 min. Then the mixture was granulated in a mortar by binder. The obtained granulates were dried in a 50°C oven for 4 hours. The final granules were then passed through a 18-mesh sieve, and the lubricant was sieved through a 40-mesh sieve onto the mixture and blended for 5 min. Finally, the granules were compressed using a single-punch tablets formation machine with a 13mm diameter biconcave punch and die set.

Carr's index: Carr's index was calculated using the equation $([p_{\text{tap}} - p_{\text{bul}}] / p_{\text{tap}}) * 100$. The bulk and tap densities were determined as follows. Each sample (20 g) was poured through a funnel into a 100-mL tarred graduated cylinder. The cylinder was then lightly tapped to collect all the powder sticking on the wall of the cylinder. The volume was read directly from the cylinder and used to calculate the bulk density. For tap density, the cylinder was tapped to attain a constant volume reading from the cylinder.

Hardness: Hardness of ten randomly selected tablets was determined. The mean hardness and coefficient of hardness variation were calculated.

Friability test: Tablet friability was measured as the percentage of weight loss of 10 tablets tumbled in a friabilator. After 4 minutes of rotation at 25 rpm, dust of tablets was removed and percentage weight loss was calculated.

HPLC analysis: The samples were determined using a Shimadzu LC-20AT HPLC (Shimadzu, Kyoto, Japan) equipped with a C-18 chromatographic column (5µm, 250 mm × 4.6 mm). The mobile phase was composed of sodium dihydrogen phosphate - methanol-isopropanol (97:2:1, V/V/V). The flow rate was 1.0mL/min. The wavelength was set at 210nm.

In vitro studies: Dissolution studies were carried out using a ZRS-8G dissolution apparatus (Haiyida, China). Test samples were tested at the paddle rotation speed of 50 rpm in 900mL distilled water at 37±0.5°C.

The sample 5ml withdrawal by suitable time interval and fresh dissolution medium were added in the each withdrawal. The samples were filtered through a membrane filter (pore size 0.45 μ m) then appropriately diluted and measured by HPLC shown above.

RESULTS AND DISCUSSION:

Effect of diluent on the qualities of pidotimod dispersible tablets: Lactose, MCC, sucrose, mannitol and starch are used as diluents to investigate effect of different contents of diluents on Carr's index, hardness, friability and dissolution. The Carr's index was found to be in the

range 10%-12% which shown good compressibility of the powder blend. Hardness (40N-50N) and friability (0.32%-0.45%) showed the good mechanical resistance of the tablets. And all the tablets had smooth surface without spots.

Another an important parameter that should be investigated was dissolution behavior. From **Table 1** we could see that all formulations had good dissolution behavior. And it also showed a decreased dissolution behavior due to increasing contents of lactose. But the contents of MCC should not be too high, for it had grittiness. Considering all these reasons, we selected F5 for future research.

TABLE 1: FORMULATIONS OF DIFFERENT DILUENTS AND RESULTS

FORMULATION INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6
Pidotimod	400	400	400	400	400	400
MCC	60	75	90	105	120	135
Mannitol	80	80	80	80	80	80
PVPP	80	80	80	80	80	80
Lactose	120	105	90	75	60	45
Aspartame	20	20	20	20	20	20
Magnesium stearate	10	10	10	10	10	10
6%PVP 50% ethanol solution	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Results						
Carr's index (%)	10.56	10.83	11.42	11.16	10.62	10.74
Dissolution (%)	75.4	79.7	84.5	86.4	85.2	89.9
Hardness (N)	40-50	40-50	40-50	40-50	40-50	40-50
Friability (%)	0.44	0.42	0.45	0.35	0.32	0.37

Effect of lubricant on the preparation of pidotimod dispersible tablets: To investigate the effect of different types of lubricants on the preparation of pidotimod dispersible tablets, we selected talc, magnesium stearate and aerosil as lubricants. In the study, the magnesium stearate in F5 was replaced by talc or aerosil with the same weight, and other components remained unchanged.

After tableting with the same method, we found that all these lubricants could make tablets with smooth surface without spots. And all tablets had no significant difference in weight, hardness and dissolution behavior. Then we chose magnesium stearate as lubricant and the content of it in each tablet was 10 mg.

Effect of disintegrant on dissolution: the influence of the contents of CMS-Na and PVPP on the dissolution of pidotimod from the tablets was investigated.

The result was shown in **Table 2**. From Table 2, we could see that the dissolution amount increased with increasing of the content of CMS-Na or PVPP in each tablet from 80mg to 120mg. And there were no significant differences in the appearance of tablets. Because tablets with CMS-Na had a little higher percentage of drug release than tablets with the same weight of PVPP and the price of PVPP was higher than CMS-Na.

We chose CMS-Na as disintegrants.

TABLE 2: FORMULATION OF DIFFERENT DISINTEGRANTS AND RESULTS

FORMULATION INGREDIENTS (mg)	F5	F7	F8	F9	F10	F11
Pidotimod	400	400	400	400	400	400
MCC	120	120	120	120	120	120
Mannitol	80	80	80	80	80	80
PVPP	80	100	120	-	-	-
CMS-Na	-	-	-	80	100	120
Lactose	60	60	60	60	60	60
Aspartame	20	20	20	20	20	20
Megnesium stearate	10	10	10	10	10	10
6%PVP 50% ethanol solution	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Results						
Dissolution (%)	85.2	89.6	96.4	87.6	91.8	97.1

CONCLUSION: The results showed that the optimum proportion was 400mg pidotimod, 120mg MCC, 80mg mannitol, 120mg CMS-Na, 60mg lactose, 20mg aspartame, 10mg magnesium stearate and 6%PVP 50% ethanol solution. Pidotimod dispersible tablets with optimum proportion showed acceptable hardness, friability, dissolution behavior. The preparation process was simple and the tablets could be prepared by ordinary tablet production equipment. So it is suitable for mass industrialized production. The final tableting formulation and the simplified process both had tremendous potentials in commercial large-scale production.

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