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In vitro and *in vivo* evaluation of novel osmotic pump tablets of isosorbide-5-mononitrate containing polyvinyl pyrrolidone (PVP) for controlled release

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A novel osmotic pump tablet with ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) as the semipermeable membrane and isosorbide-5-mononitrate (5-ISMN) as the model drug was formulated in this study. Zero order release kinetics were attained by avoiding aging during storage. Drug release increased with an increase in the percentage of PVP K30 in the semipermeable membrane. However, drug release decreased with increased coating weight. Drug release rates decreased continuously for tablets coated with EC/PEG4000 and cellulose acetate (CA)/PEG4000. This tendency was more marked with longer storage time. However, there was little change in drug release rates for tablets with a semipermeable membrane of EC/PVP K30 at 6, 12 or 24 months. The weight loss test also validated the results mentioned above. The relative bioavailability of the osmotic-pump tablets against the reference formulation in single and multiple dose regimens was 116.7 and 106.5, respectively. This means that the bioavailability of osmotic pump tablets using PVP as the plasticiser was equal to that of the reference formulation. In general, 5-ISMN osmotic pump tablets with a semipermeable membrane composed of EC/PVP K30 may be useful in providing constant drug delivery with minimum fluctuations during longer storage time.

1. Introduction

Isosorbide-5-mononitrate (5-ISMN) is a nitrate drug used for the prophylaxis angina pectoris by allowing the blood vessels to relax and widen to improve blood circulation; that is it is taken in order to prevent or at least reduce the occurrence of angina (Fotaki et al. 2005). It would be anticipated that 5-ISMN could maintain its effect over a relatively long time. However, the original formulation in clinical use had to be taken every eight to twelve hours. The drawbacks included wide fluctuations of plasma concentration, high C_{max} and severe side effects. Sustained-release tablets of 5-ISMN which were developed later were taken once daily. This promoted patients' compliance, and decreased the side effects to some extent. However, its release rate was not constant. Moreover, the rates of release and absorption were influenced significantly by patients' gastrointestinal fluids, and, therefore, the plasma concentration was unpredictable and inter-individual differences were marked.

Osmotic systems utilize osmotic pressure as the driving force for controlled delivery of drugs. An osmotic pump consists of an osmotic core coated with a semipermeable membrane. The dosage form imbibes water at a rate determined by the fluid permeability of the membrane and the osmotic pressure of the core formulation after coming into contact with aqueous fluids (Verma et al. 2002). Therefore, the saturated drug solution inside the tablet is released from the pore. The volume released is equal to that of the water penetrating into the tablet within a certain time. Therefore, it can release drug at a constant rate (Liu and Wang 2008). If controlled osmotic pump tablets of 5-ISMN were developed, it could maintain its therapeutic effects over a longer period, minimising fluctuation of plasma concentration, side effects, and individual differences.

Semi-permeable membrane play a significant role in the controlled-release of drugs in oral osmotic pump formulations. Water permeability differs depending on the composition of the semi-permeable membrane (Makhija and Vavia 2003). The most common semi-permeable membranes include cellulose acetate (CA) (Zentner et al. 1985), ethyl cellulose (EC) (Hjartstam and Hjertberg 1998), cellulose acetate plus polyethylene glycol (PEG) (Chou et al. 2007), ethyl cellulose plus PEG (Liu and Che 2006; Liu and Xu 2008), etc. Immediately after preparation, release profiles are stable and fit a zero order model. After storage for a considerable time, the amount released decreases significantly, due to aging.

The aim of this study was to develop novel, single-compartment, controlled release osmotic pump tablets of 5-ISMN, which maintain their constant release characteristics over their shelf life and have no restriction as to storage time. The semi-permeable membrane of the 5-ISMN osmotic pump tablets consisted of EC and polyvinyl pyrrolidone to avoid aging. Moreover, it gave a longer circulation time of the drug in plasma and maintained a steady plasma concentration.

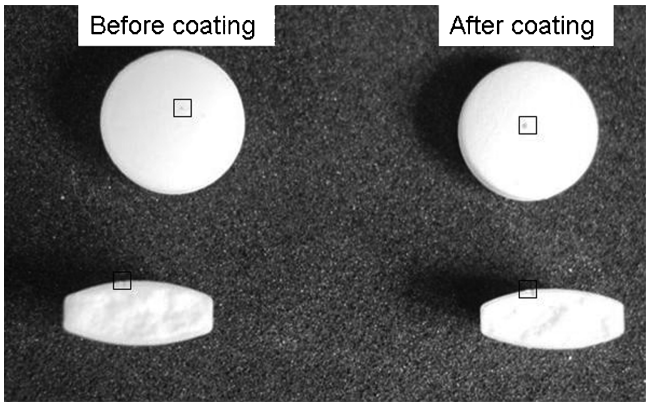

Fig. 1: Appearance of 5-ISMN osmotic pump tablets before and after coating

2. Investigations, results and discussion

2.1. Influence of semipermeable membrane on drug release

5-ISMN osmotic pump tablets coated with Opadry ® II as a thin membrane were more white and compact than uncoated tablets (Fig. 1).

Different ratios of EC and PVP K30 had an obvious effect on drug release. Drug release increased with an increase in the percentage of PVP K30 (Fig. 2). This may be due to the soluble plasticizer, PVP K30, dissolving on contact with water. Thus, micropores formed in the semi-permeable membrane and water could enter the tablet core to facilitate drug release. The more PVP K30 dissolved, the better was the membrane permeability.

The effects of different semi-permeable membranes on drug release were investigated. The average coating weight gain of EC + PEG 4000 (30:21, w/w), CA + PEG 4000 (30:16, w/w) and EC + PVP 30 (30:20, w/w) was 7% and their pore diameter was 9 nm. After optimization, the release profiles were similar for semi-permeable membranes composed of EC + PEG 4000 (30:21, w/w) CA + PEG 4000 (30:16, w/w) and EC + PVP K30 (30:20, w/w) (Fig. 3). Their major difference was whether the release profiles decreased after storage for a long time.

The combination of EC and PVP is the most common membrane material for sustained release micropellets. There have been no previous reports about their combined use for preparation of controlled osmotic pump tablets. The release mechanisms of sustained release micropellets and controlled osmotic tablets are clearly different. The release mechanism of sustained-release micropellets is diffusion. Because the size of sustained-release micropellets is so small and the relative surface area large, an appropriate diffusion coefficient of the membrane is important for drug release (Lin 1993). Its release pattern fits the Higuchi equation (Baidya et al. 1999). The most important characterics is that the membrane of micropellets is not semi-permeable. It can imbibe water and release drug at the same time. In contrast, controlled osmotic pump tablets are based on the osmotic pressure principle (Marucci et al. 2010). The membrane only permits water to pass through, and drug can only be released from the predetermined micropores in the membrane. Its release profile fits zero-order kinetics. In general, EC as a semipermeable membrane containing PVP as plasticizer is a new idea for preparing osmotic pump formulation and avoiding the aging phenomenon.

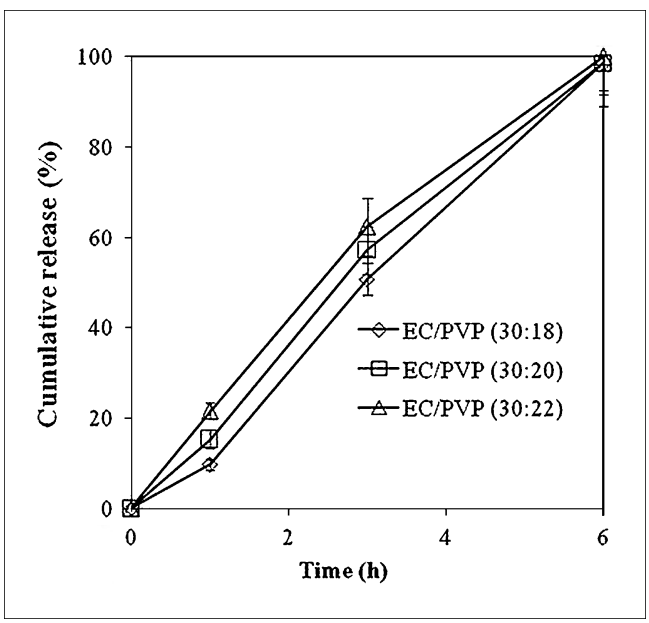

Fig. 2: Influence of different ratios of EC/PVP K30 on drug release

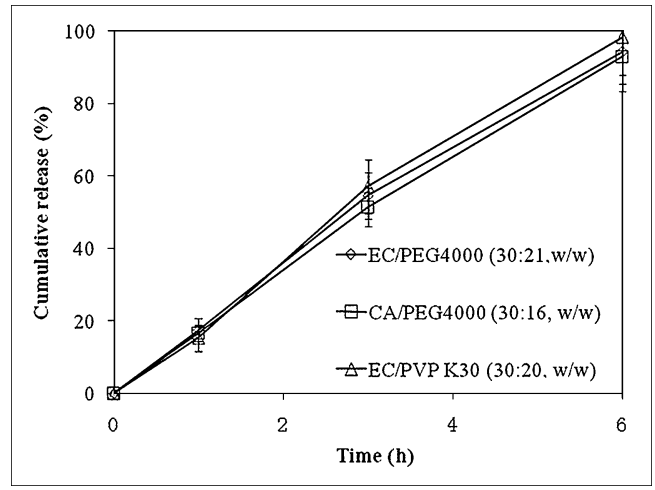

Fig. 3: Influence of different semipermeable membranes on drug release

2.2. Influence of coating weight gain on drug release

Coating weight gain may also affect drug release. In this study, weight gains of 5, 7 and 9% (w/w) of EC + PVP K30 (30:20, w/w) were used for coating, and the membrane pore size was +0.6 mm. Drug release decreased with increasing coating weight gain (Fig. 4). The relationship between them was negative. This may be due to the increased thickness of the semipermeable membrane causing decreased permeability. Hardly any water enters the tablet core through the surface pores. Therefore, the drug did not dissolve to form a saturated solution and so was hard to release from the core. Finally, the release profiles decreased. However, there is a dilemma regarding the weight gain of the semipermeable membrane. If the weight gain was too low, the membrane was too thin to form a continuous coating. This may cause membrane rupture. If the weight gain increases too much, the coating process may be too long and the cost may be too expensive. As a result, it is important to optimize the weight gain ratio to obtain desirable release rates.

2.3. Stability study

The release profiles of 5-ISMN osmotic pump tablets coated with different semi-permeable membranes were evaluated at predetermined time points. Drug release rates decreased continuously for the tablets coated with EC/PEG4000 and CA/PEG4000 (Fig. 5 A and B). The tendency to decrease was more apparent with a longer storage time. This resulted

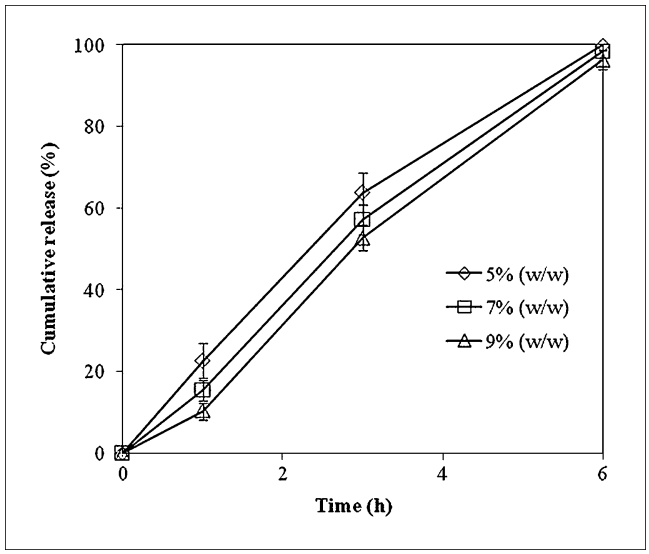

Fig. 4: Influence of coating weight gain on drug release

from aging. However, drug release rates changed little at 6, 12, 24 months for the semipermeable membrane of EC/PVP K30 (Fig. 5 C). The semipermeable membrane was composed of membrane-forming polymers – CA or EC (not water-soluble) - and plasticizers – PEG or PVP (water-soluble). If the plasticizers combined with polymers during long-term storage, the permeability of the membranes would decrease due to the lower ratio of soluble components. This would result in less water entering the tablet core and a lower drug release rate. However, EC did not react with PVP and the membrane permeability did not change. Therefore, they could overcome aging.

2.4. Weight loss of semipermeable membrane

The designed weight loss of the membrane could affect the membrane permeability by the interaction of the plasticiser and membrane polymers. If the plasticiser and the polymers conjugated continuously during storage, the ratio of soluble components would decrease. In this case, weight loss would decrease. On the other hand, the weight loss would not change if the plasticiser and the polymers did not interact. Therefore, the weight loss test could simulate membrane aging. The weight loss ratio of a semipermeable membrane composed of EC/PEG4000 and CA/PEG4000 decreased gradually with longer storage time (Fig. 6). This demonstrated that the membrane polymers interacted with the plasticiser-PEG in the two semipermeable membranes mentioned above. As a result, hole formation caused by autolysis decreased. This resulted in reduced membrane permeability and drug release rate. This corresponded with the stability study (Fig. 5 A and B). In comparison, the weight loss

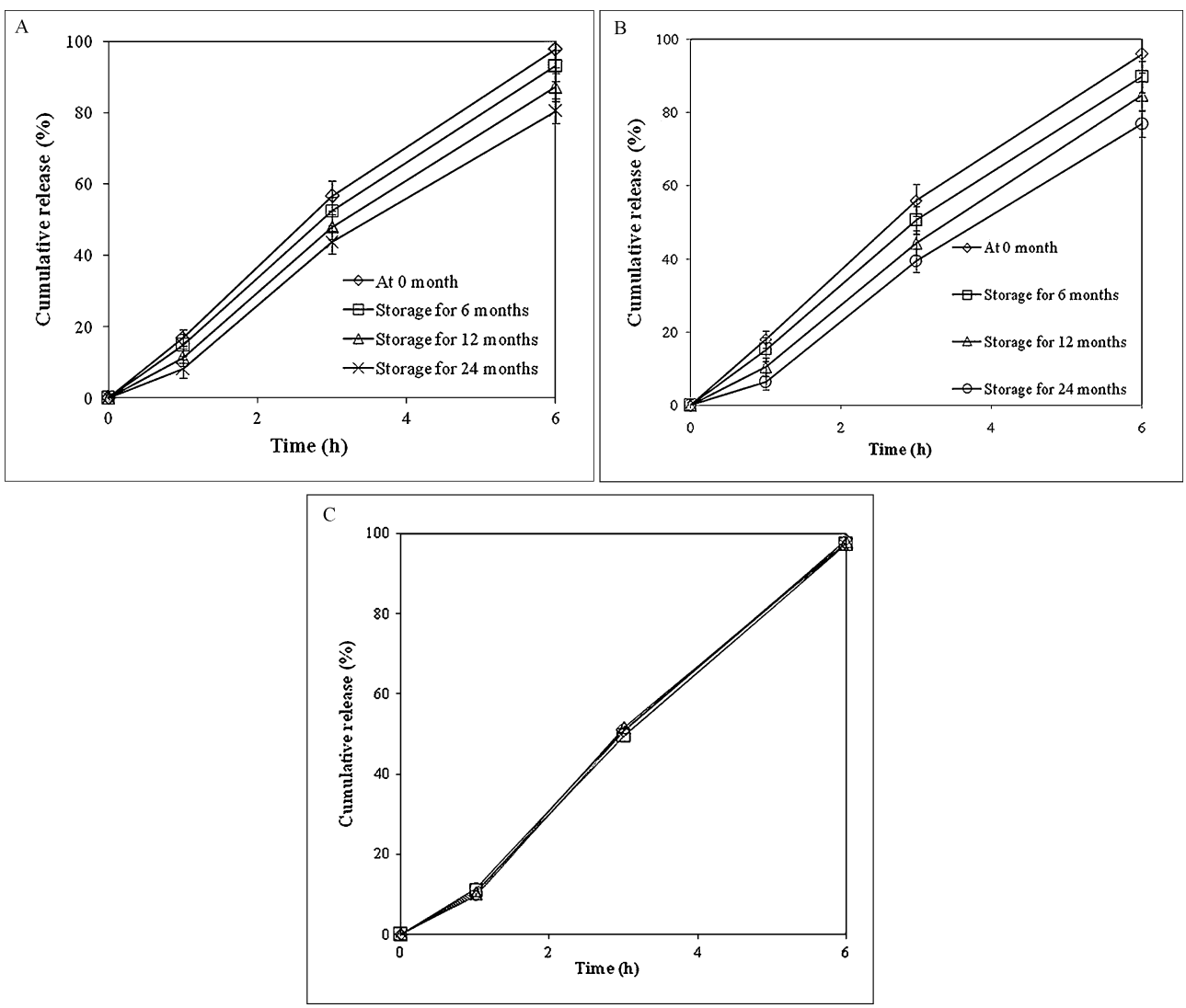

Fig. 5: Drug release profiles for stability evaluation. A EC/PEG4000; B CA/PEG4000; C EC/PVP K30

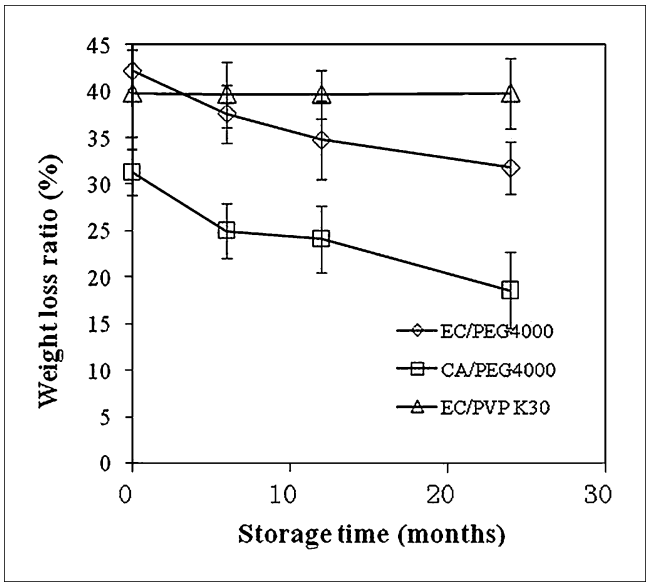

Fig. 6: Weight loss ratio after storage for different times

ratio of the membrane composed of EC/PVP K30 did not change during storage. This demonstrated that PVP hardly reacted with EC and only acted as a hole-forming agent. Therefore, the content of soluble excipients kept constant and the drug release rate did not change either. This also corresponded with the stability study (Fig. 5 C). In general, PVP could avoid the aging of the semipermeable membrane efficiently.

2.5. Bioavailability study

Plasma 5-ISMN concentration profiles from single and multiple dose experiments with the reference formulation and 5-ISMN osmotic pump tablets are shown in Fig. 7. For the single dose regimen, the Cmax values were 533.82 ± 143.24 ng/ml (Tmax: 5.36 ± 1.68 h) for the reference formulation – Xinkang™ sustained release tablets - and 496.91 ± 147.12 ng/ml (Tmax: 5.91 ± 1.44 h) for the 5-ISMN osmotic pump tablets (Table 1). No significant differences in Cmax (bilateral one-side test) and Tmax (Wilcoxon rank sum test) values were observed between the two formulations. The relative bioavailability of the osmotic-pump tablets against the reference formulation was 116.7%. This means that the bioavailability value of the osmotic pump tablets using PVP as the plasticiser was equal to that of the reference formulation.

In the multiple dose regimen, the Cmax values were 571.43 ± 190.51 ng/ml (Tmax: 3.55 ± 1.47 h) for the reference formulation – Xinkang™ sustained release tablets - and 584.95 ± 144.46 ng/ml (Tmax: 4.52 ± 1.66 h) for the 5-ISMN osmotic pump tablets (Table 2). No significant differences in the Cmax (Bilateral one-side test) and Tmax (Wilcoxon rank sum test) values were observed between the two formulations. The relative bioavailability of the osmotic-pump tablets against the reference formulation was 106.5%. This also confirms the results mentioned above. In general, the controlled osmotic pump 5-ISMN tablets were bioequivalent with the marketed sustained-release tablets, with the plasma concentration of the former more steady. This guarantees that the controlled osmotic pump tablets are more efficient.

2.6. Conclusion

The formulated 5-ISMN controlled osmotic pump tablets with EC/PVP K30 as the semipermeable membrane did not age during storage and may be safer with ethanol in place of acetone as the coating solution. Therefore, it may be useful for providing constant drug delivery with minimum fluctuations.

3. Experimental

3.1. Materials

5-ISMN and the sustained release 5-ISMN tablets (reference formulation) were all purchased from Lunan Pharmaceutical Group (Shandong Province, China). Nitroglycerin was supplied by the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Polyvinyl pyrrolidone (PVP) K30 and PEG (polyethylene glycol) 4000 were obtained from International Specialty Products, Inc. (New Jersey, US.A) and Dow Chemical Company (Beijing, China), respectively. Cellulose acetate was from Eastman Chemical Company (Tennessee, USA). Sucrose was from Sifang Industry Co., Ltd. (Xinjiang Province, China). Magnesium stearate and silicon dioxide were from Huzhou Zhanwang Pharmaceutical Company (Jiangsu Province, China). Ethylcellulose N100 was from Ruitai Chemical Industry Co., Ltd (Shandong Province, China). Methanol (HPLC grade) was purchased from Merck (Darmstadt, Germany). All the other chemicals used were of analytical grade. Human studies were carried out in accordance with the Declaration of Helsinki.

3.2. Preparation of controlled release tablets

5-ISMN (40 g) and 190 g sucrose were sieved, weighed, and mixed in a wet type granulator (SMG2–6, Chongqing Enger Granulating & Coating Technology Co., Ltd., China) for 10 min. Subsequently, an 8% (w/v) ethanol

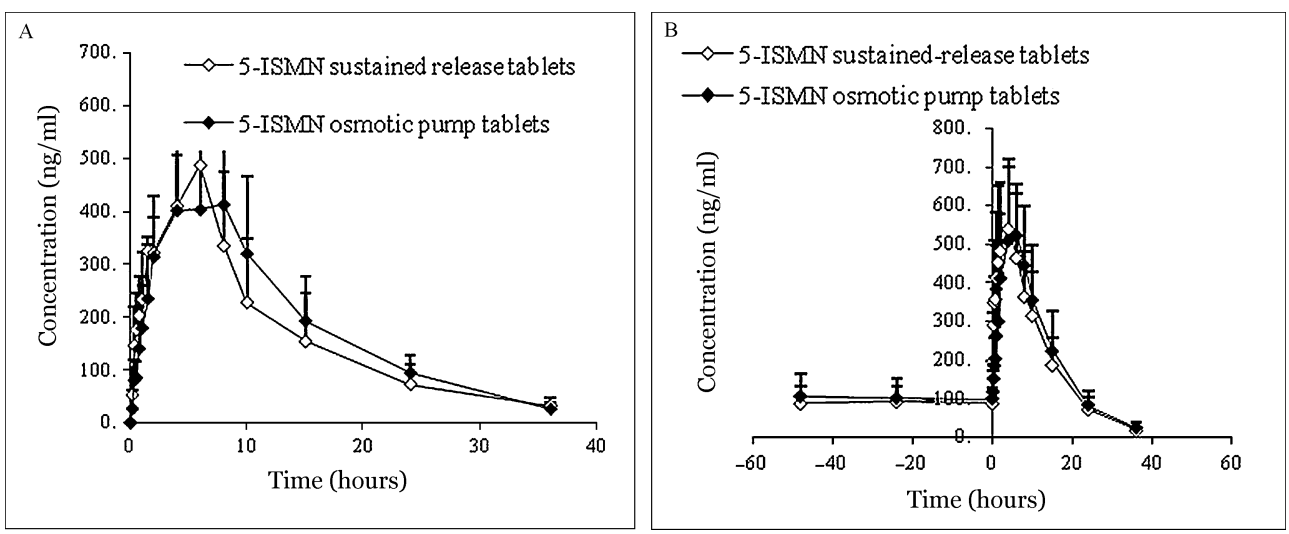

Fig. 7: Plasma concentration – time profiles of reference formulation and osmotic pump tablets. A Single-dose design; B Multiple-dose design

Table 1: Mean pharmacokinetic parameters in volunteers following oral administration of single doses of osmotic pump tablets and sustained release tablets of 5-ISMN

Parameters	Single dose regimen	
	Osmotic pump tablets	Sustained release tablets
C_{max} (ng/ml)	596.91 ± 147.12	533.82 ± 143.24
T_{max} (h)	5.91 ± 1.44	5.36 ± 1.68
$t_{1/2}$ (h)	6.95 ± 0.69	6.56 ± 2.59
$AUC_{(0-t)}$ (ng/ml*h)	6708.05 ± 1559.16	5956.28 ± 2068.30
$AUC_{(0-\infty)}$ (ng/ml*h)	6937.45 ± 1601.83	6191.02 ± 2186.00
Relative bioavailability (%)	116.7 ± 15.6	

Table 2: Mean pharmacokinetic parameters in volunteers following oral administration of multiple doses of osmotic pump tablets and sustained release tablets of 5-ISMN

Parameters	Multiple dose regimen	
	Osmotic pump tablets	Sustained release tablets
C_{max} (ng/ml)	584.95 ± 144.46	571.43 ± 190.51
T_{max} (h)	4.52 ± 1.66	3.55 ± 1.47
$t_{1/2}$ (h)	6.94 ± 1.85	6.56 ± 0.89
AUC_{ss} (μg/ml*h)	7022.30 ± 2231.33	6695.88 ± 2163.34
Relative bioavailability (%)	106.5 ± 18.0	

solution of PVP K30 were added to the mixture and wet granulation was carried out. The granules obtained were dried at 40 °C and screened through the sieve with an 850 μm mesh. 3 g magnesium stearate and 1 g silicon dioxide were mixed together with the granules and the resulting mixture was compressed into tablets using a rotary tableting machine (ZPW23, Shanghai Tianxiang & Chentai Pharmaceutical Machinery Co., Ltd., China) with 9-mm diameter punches. The tablets hardness was maintained within a range of 5–7 $kg \cdot cm^{-2}$. The tablets obtained were coated with semipermeable membrane using different coating solutions (Table 3). The coating process was performed using a high efficiency coating machine (BG1–5, Beijing Institutes of Aviation Manufacturing Technology, China) and the coating conditions were as follows: inlet pressure 3 $kg \cdot cm^{-2}$, spray pressure 1 $kg \cdot cm^{-2}$, temperature 40 ± 2 °C and spray rate 13 ± 1 $mL \cdot min^{-1}$. Average weight gain after coating was controlled at different levels to investigate the influence of coating thickness on 5-ISMN release. The coated tablets were kept at 40 °C for 12 h to remove residual solvent and promote the coalescence of the coating membrane. Then a 0.6 mm orifice for drug release was drilled using a laser punching machine (RC-YW-30, Nanjing Ruichi Electronic Technology Co. Ltd., China) on one side of the tablets. The outer coating solution containing Obady II (10%, w/v) was sprayed on to the tablets using a high efficiency coating machine. Coating was continued until a weight gain of 3% (w/w) was achieved.

3.3. In vitro drug release study and stability study

In vitro release of 5-ISMN from the tablets was studied using a paddle type apparatus (Radio Factory of Tianjin University, Tianjin, China) with 500 ml of dissolution medium (deionized water) at 37 ± 0.5 °C, and a stirring rate of 50 rpm. 5 ml of solution were withdrawn and replaced with the same volume of fresh medium at 1, 3 and 6 h. The samples obtained were filtered (0.45 μm) immediately and analyzed by HPLC, using an injection volume of 20 μL. All experiments were repeated for three times. The stability study was conducted in a constant temperature and humidity chamber for 24 months. Dissolution tests were performed at 0, 6, 12 and 24 months using the method described above. HPLC determinations were performed on an L-2130 Hitachi HPLC system (Japan), consisting of an L-2130 pump, L-2400 UV detector, and Hitachi D-2000 chromatographic workstation software. Separations were performed with a Diamonsil C_{18}-ODS column (4.5 mm × 150 mm, 5 μm). 5-ISMN was measured at 210 nm with a mobile phase of methanol/water (25:75, v/v) at room temperature. The flow rate was 1.0 ml min^{-1}.

Table 3: Composition of coating solution

Ingredients	Coating solution				
	A	B	C	D	E
Ethylcellulose N100 (g)	30	–	30	30	30
Cellulose acetate (g)	–	30	–	–	–
PVP K-30 (g)	–	–	18	20	22
PEG4000 (g)	21	16	–	–	–
Acetone (ml)	–	900	–	–	–
Ethanol (ml)	900	–	1000	1000	1000
Water (ml)	100	100	–	–	–

3.4. Weight loss of semipermeable membrane

Film coating of the 5-ISMN tablets was removed, followed by cautiously peeling away the semipermeable membrane. Then the semipermeable membrane was brushed gently to remove residual powder and weighed accurately (W_0). The membrane obtained was put into a basket type apparatus (Radio Factory of Tianjin University, Tianjin, China) with 500 ml of dissolution medium (deionized water) at 37 ± 0.5 °C, and stirred at 50 rpm. Semipermeable membranes were taken from the basket at 1 h and 2 h, respectively. The membranes obtained were dried at 50 °C and then weighed after cooling to room temperature (W_T). Percentage weight loss of the semipermeable membrane was calculated according to the following formula:

$$\text{Weight loss } (\%) = (1 - W_T / W_0) \times 100\%$$

The weight loss of the semipermeable membrane was conducted together with the stability study of the 5-ISMN controlled release tablets for 24 months. Determinations were performed at 0, 6, 12 and 24 months using the method described above.

3.5. Bioavailability studies

3.5.1. Subjects

Healthy male volunteers aged 20 to 27 years with body mass index from 19 to 24 participated in the study. Volunteers were excluded from the study if they had abnormal results of medical examination. All the volunteers selected were nonsmokers and non-alcoholics. They were required to abstain from all drugs and from alcoholic or caffeinated beverages for two weeks before starting the study and throughout the whole process. The study was approved by the Center for Drug Evaluation (China).

3.5.2. Protocol

The study design was a single-dose, fasting, 2-way crossover design. The 22 human volunteers were assigned randomly to two equal groups. A single dose of the test formulation (5-ISMN controlled osmotic pump tablets,

40 mg) or the reference formulation (5-ISMN sustained release tablets, 40 mg) were administered orally to the volunteers with 200 mL of water. Volunteers were required to take no food or drink for 2 h after dosing and were provided with a standard meal at 4 and 10 h after administration of the drug. Blood samples were collected from each volunteer's forearm cubital vein before administration and at 0.5, 0.75, 1, 1.5, 2, 4,6, 8, 10, 15, 24, and 36 h after dosing. The blood samples were immediately centrifuged at 1000 × g at 4 °C and then the plasma was separated and stored at −20 °C until analyzed. A 2-week washout period was allowed according to the $t_{1/2}$ of 5-ISMN and the alternativee formulation was given after administration of the first dose. The multiple-dose experiment was a fasting, 2-way crossover design. Twenty-two human volunteers were randomly assigned to two equal groups. The test formulation (5-ISMN controlled osmotic pump tablets, 40 mg) or the reference formulation (5-ISMN sustained release tablets, 40 mg) were administered orally to the volunteers with 200 mL of water. Volunteers were required to take no food or drink for 2 h after dosing and were provided with a standard meal at 4 and 10 h after administration of the drug. Blood samples were collected from each volunteer's forearm cubital vein before administration and at 0.5, 0.75, 1, 1.5, 2, 4,6, 8, 10, 15, 24, and 36 h after dosing. The blood samples were immediately centrifuged at 1000 × g at 4 °C and then the plasma was separated and stored at − 20 °C until analyzed. A 2-week washout period was allowed according to the $t_{1/2}$ of 5-ISMN and the alternative formulation was given after administration of the last dose.

3.5.3. Determination of plasma 5-ISMN concentration

Quantification of 5-ISMN in plasma samples was analyzed using a gas chromatograph (GC) with an electron capture detector (ECD) (GC-ECD) under the following operating conditions. A Shimadzu apparatus equipped with a split/splitless injector and a ZB-1 (100% dimethyl-polysiloxane) capillary column (30 m, 0.25 mm id, 0.25 μm film thickness; Agilent Technologies, Inc., California, USA) were used. Nitrogen was used as the carrier gas with a flow rate of 2 mL·min^{-1}. The column temperature was programmed to an initial 140 °C for a 6 min hold, then increased at 50 °C·min^{-1} to 210 °C and stopped immediately. Injector and detector temperatures were set at 200 °C and 220 °C, respectively. The split ratio was 12:1. A Chromato-Solution Light chromatographic workstation was used throughout the entire experiment for data acquisition and processing.

Blood samples containing 5-ISMN were treated as follows. A 200-μl aliquot of plasma sample was thoroughly mixed with the nitroglycerin standard solution in methanol as the internal standard (2 μg·ml^{-1}, 10 μl). Ethyl acetate (1 ml) was added to the above sample, vortexed for 3 min, and centrifuged at 5000 × g for 10 min. The supernatant was pipetted into a clean tube and evaporated to dryness under a gentle stream of nitrogen. The residue was redissolved with methanol (70 μl) followed by centrifuging for 5 min at 5000 × g. The supernatant was transferred to a tube and 1 μl was injected into the gas chromatograph.

3.6. Pharmacokinetic and statistical analyses

DAS 2.0 software was used to calculate and analyze the pharmacokinetic parameters. $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were calculated by the linear trapezoidal rule and extrapolation to infinity, respectively. C_{max} and T_{max} were obtained directly from the 5-ISMN plasma concentration-time curve. $t_{1/2}$ was estimated using the formula $t_{1/2} = 0.693/k_e$. The relative bioavailability (F) of the test tablets (5-ISMN controlled release tablets) to the reference tablets was calculated using the following equation:

$$F = AUC_{0-\tau(\text{test})}/AUC_{0-\tau(\text{reference})} \times 100\%$$

A nonparametric test (Wilcoxon rank sum test) was used to evaluate the significance of T_{max}. A bilateral one-side test was performed on the log-transformed data of AUC and Cmax to assess the bioequivalence of the two formulations. If the 90% confidence intervals for AUC and Cmax were within the statistical intervals (0.80–1.25) and (0.75–1.33) respectively, the two formulations would be considered bioequivalent.

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