International Journal of Pharmaceutics 402 (2010) 129–139

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Design and evaluation of a novel formulation prediction system

Jin Guan[a], Rongwu Xiang[b], Yusheng Pan[a], Hao Pan[a], Xiangdong Su[c], Liying Zhou[a], Yuni Cui[a], Weisan Pan[a,*]

[a] Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenhe District, Liaoning, Shenyang 110016, China
[b] Mathematics Teaching & Research Section, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang 110016, China
[c] Research & Development Center of CAD/CAM, Shenyang Ligong University, 6 Nanpingzhong Road, Shenyang 110168, China

ARTICLE INFO

Article history:
Received 9 July 2010
Received in revised form 17 August 2010
Accepted 28 September 2010
Available online 7 October 2010

Keywords:
Formulation prediction system
Ternary-component diagram
Optimal formulation region
Triangular prism model
Interpolation algorithm
Monolithic osmotic pump tablets

ABSTRACT

Purpose: The purpose of this study is to design and evaluate a novel formulation prediction system for formulation study of monolithic osmotic pump tablets (MOPTs).
Methods: Ternary-component diagram was originally brought forward to evaluate MOPTs formulations. Optimal formulation regions were delimited in ternary-component diagrams. Water-insoluble drug gliclazide was chosen as a model drug for selecting most suitable suspending agent. With five model drugs, we obtained five ternary-component diagrams. By MATLAB® software, a triangular prism model was then established regarding doses as vertical coordinate and the five diagrams as cross-sections, with the formation of an optimal formulation channel in it, followed by the design of formulation prediction software (FPS 1.0). The practicality of the system was finally validated.
Results: After entering the drug information, we immediately obtained the optimal formulation region for preparing MOPTs with interpolation algorithm. The dissolution test results of the four randomly selected formulations all met the evaluating conditions.
Conclusions: Ternary-component diagram is useful for MOPTs formulation optimization. The predictive ability of the system is tentatively confirmed and the experiment efficiency is greatly improved.

1. Introduction

Osmotic pump tablet (OPT) is one of the most ideal dosage forms for orally controlled drug delivery. It has certain advantages: zero-order release rate; independence of the factors of release media, pH and food; and good in vitro/in vivo correlation (Gan et al., 2002). Therefore it has been widely studied. Theeuwes (Theeuwes, 1975) introduced the elementary osmotic pump (EOP) in the 1970s and brought forward its basic theory. However, EOP is only suitable for water-soluble drugs. The problems caused by drugs with low water solubility, such as inadequacy of cumulative release and lacking zero-order release character cannot be solved by EOP. Two-compartment (Theeuwes, 1978), two-layer push–pull (Cortese and Theeuwes, 1982) and three-layer (Stephens and Wong, 1989) osmotic pump tablets have been developed to overcome the limitations of EOP. Nevertheless, all of those osmotic tablet systems have showed a common shortcoming, i.e. certain sophisticated technique is demanded. Monolithic osmotic pump tablets (MOPTs) which consist of osmotic and suspending agent in the core tablets can be prepared by simple technology. They have been proved to be able to deliver water-insoluble drugs by suspending them in the core tablets. Therefore, finding an appropriate polymer as the suspending agent is critical. Polyethylene oxide (PEO) has been widely used in drug delivery systems of multiple-layer osmotic pump tablets, gel-matrix tablets and bioadhesive dosage forms (John et al., 2008; Kuczynski et al., 1996; Yang et al., 1998; Kim, 1995; Hiroyuki et al., 2008; Hülya and Olgun, 2001; Tetsuya et al., 1999). Liu et al. (Liu et al., 2000) used PEO as a suspending agent which was expected to absorb water from the medium to expand and suspend with drug, to prepare Nifedipine MOPTs.

For MOPTs containing water-insoluble drugs, the formulation design and optimization need lots of experiments to ensure the ultimate cumulative drug release and correlation coefficient of drug release profile. In this study the MOPTs formulations were simplified into three components—model drug, PEO and NaCl, and the coating conditions were fixed. A new method was brought forward to evaluate MOPTs formulations—ternary-component diagram of MOPTs, based on the principle of pseudo-ternary phase diagrams of micro-emulsion (Cirri et al., 2007). The right side line of the triangle represents the percentage of PEO; the left one indicates the percentage of NaCl; and the base line represents the model drug content. Therefore this triangle contains all the formulations which

* Corresponding author. Tel.: +86 24 23953241; fax: +86 24 23953241.
E-mail address: ppwwss@163.com (W. Pan).

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doi:10.1016/j.ijpharm.2010.09.036

are composed of model drug, PEO and NaCl. According to the evaluating conditions, i.e. the cumulative release greater than or equal to 75%, the correlation coefficient of drug release profile greater than or equal to 0.99 and the period of drug delivery up to 10 or 12 h, the optimal formulation regions were delimited in ternary-component diagrams. In this research, water-insoluble drug gliclazide was firstly chosen as a model drug and eight sorts of PEO with different molecular weight (M_w)—WSR N10, WSR N80, WSR N750, WSR N1105, WSR N12K, WSR N60K, WSR 301 as well as WSR 303 were selected as the suspending agent to draw eight ternary-component diagrams. Accordingly the PEO which is most suitable for water-insoluble drug MOPTs was chosen. Then using this PEO as suspending agent and using gliclazide, gliquidone, theophylline, aceclofenac as well as gatifloxacin as water-insoluble model drugs (the doses are 30 mg, 60 mg, 100 mg, 150 mg and 200 mg, respectively), we drew five ternary-component diagrams. A triangular prism model was then established regarding doses as the vertical coordinate and five ternary-component diagrams as the cross-sections. Using MATLAB® software for programming, we designed formulation prediction system for MOPTs (FPS 1.0). The purpose of this system is to immediately obtain the optimal formulation region for preparation of MOPTs with the method of interpolation algorithm after entering the dose of some water-insoluble drug. Therefore the experiment efficiency will be greatly improved. Compared with other statistical prediction and optimization systems for the same application, this system is convenient and efficient, and no artificial calculations are needed. Furthermore, what it predicts is an optimal formulation region rather than a single formulation. This will facilitate R & D and production.

2. Materials and methods

2.1. Materials

Gliclazide, gliquidone, theophylline, aceclofenac, gatifloxacin, dextromethorphan hydrobromide, acyclovir, actarit, famotidine and azithromycin (all NF) were, respectively, purchased from Hengshuo Chemical Co., Ltd. (Wuhan, China), Yuancheng Technology Development Co., Ltd. (Wuhan, China), Hezhong Bio-Chemical Co., Ltd. (Wuhan, China), Yuancheng Technology Development Co., Ltd. (Wuhan, China), Qianjiang Pharmaceutical Co., Ltd. (Qianjiang, China), Galaxy Chemical Co. Ltd. (Wuhan, China), Teyer Pharmaceutical Co., Ltd. (Tianmen, China), Guangzhou Institute of Pharmaceutical Industry (Guangzhou, China), Yaoda Pharmaceutical Co., Ltd. (Shenyang, China) and Mu Danjiang Pharmaceutical Co., Ltd. (Mu Danjiang, China). Polyethylene oxide (PEO, NF) with M_w of 100,000 (WSR N10), 200,000 (WSR N80), 300,000 (WSR N750), 900,000 (WSR 1105), 1,000,000 (WSR N12K), 2,000,000 (WSR N60K), 4,000,000 (WSR 301) and 7,000,000 (WSR 303) was provided from Dow Chemical Co. (New Jersey, U.S.A.). NaCl was obtained from Bodi Chemical Co. (Tianjin, China). Cellulose acetate (CA, 54.5–56.0 wt.% acetyl content) was from Sinopharm Chemical Reagent Co. (Shanghai, China). Acetone, polyethylene glycol 4000 (PEG 4000, average molecular weight) were from Yuwang Chemical Reagent Co. (Shandong, China). All the chemicals used were of analytical grade.

2.2. Preparation of MOPTs

The active ingredients, PEO and NaCl were passed through a 100 mesh screen, respectively. Then they were precisely weighed with an electronic balance (Shanghai Minqiao Precise Science Instrument Co., Shanghai, China) and mixed artificially in a plastic bottle. Then the resultant powder mixture was compressed into tablets by a single-punch tableting machine (Shanghai no. 1 Pharmaceutical Device Co., Shanghai, China) using different diameter concave punches according to the core tablet weight. The hardness of the core tablets was kept at 7–9 kg by a hardness tester (Shanghai Huanghai Drug Inspection Instrument Co., Shanghai, China). CA in acetone (3%, w/v) containing plasticizer PEG-4000 (0.6%, w/v) was used as coating solution. The coating was carried out in a coating pan (Shanghai Huanghai Drug Inspection Instrument Co., Shanghai, China) with interior temperature of 30 °C, rotating rate of 30 rpm and spray rate of 50 g/min. The coated tablets were then dried at 50 °C for 24 h to remove the residual solvent before an orifice was drilled by a laser drilling machine (JK-30-M, Nanjing Rich Electronic Technology Engineering Co., Nanjing, China).

2.3. In vitro dissolution test

In vitro dissolution test was conducted in a dissolution apparatus (RCZ-6B, Shanghai Huanghai Drug Inspection Instrument Co., Shanghai, China). Temperature of the test was maintained at (37 ± 0.5) °C. The dissolution method, stirring speed and dissolution mediums varied for different active ingredients according to the USP and references (Table 1). 5 ml of solution were withdrawn and the same volume of fresh medium was added at 2, 4, 6, 8, 10 and 12 h, respectively. Then the solution was filtered through a 0.45 μm membrane filter immediately before diluted if necessary and the drug content was determined using an UV-9100 spectrophotometer (Beijing Beifenruili Analytic Instrument Co., Beijing, China). The mean of six determinations was used to calculate the amount of drug released from the samples.

2.4. Drawing of ternary-component diagrams of MOPTs

Based on preliminary experiments, some points in the ternary-component diagram were chosen to design formulations followed by tableting, coating and in vitro dissolution tests mentioned above. If the dissolution test results satisfied the evaluating conditions as follows: cumulative release greater than or equal to 75%, correlation coefficient of drug release profile greater than or equal to 0.99 and the period of drug delivery up to 10 or 12 h, the formulations at these points were estimated as optimal and acceptable ones. Otherwise they were not. This is called the trial-and-error approach (since there are hundreds of formulation points in this research, experimental data will not be summarized). More acceptable points were selected until all the optimal formulation points were connected to form an optimal formulation region. The percentage of the active ingredient should be in an appropriate range to make the weight of core tablets between 700 mg and 200 mg for the convenience of oral administration.

2.5. Selection of most suitable PEO for water-insoluble drug MOPTs

Water-insoluble drug gliclazide was firstly chosen as the model drug and eight sorts of PEO with different M_w—WSR N10, WSR N80, WSR N750, WSR N1105, WSR N12K, WSR N60K, WSR 301 as well as WSR 303 were selected as the suspending agents to draw eight ternary-component diagrams. The PEO corresponding to the ternary-component diagram which had the largest optimal formulation region was regarded as the most suitable PEO for water-insoluble drug MOPTs.

2.6. Preparation of ternary-component diagrams of five model drugs with different doses

Using the selected PEO as suspending agent, MOPTs for different model drugs were prepared. Gliclazide, gliquidone, theophylline, aceclofenac and gatifloxacin were chosen as water-insoluble model

Table 1
Dissolution methods, stirring speed and dissolution mediums of MOPTs for different active ingredients.

Drug name	Dissolution method	Speed (rpm)	Medium	Volume (mL)
Gliclazide	II (paddle)	50	Phosphate buffer, pH 7.4	900
Gliquidone	II (paddle)	100	0.4% SDS aqueous solution	900
Theophylline	II (paddle)	50	SGF without enzyme, pH 1.2	900
Aceclofenac	I (basket)	100	Phosphate buffer, pH 6.8	900
Gatifloxacin	II (paddle)	100	0.1 N HCl	900
Dextromethophan HBr	I (basket)	50	0.01 N HCl	900
Acyclovir	II (paddle)	50	0.1 N HCl	900
Actarit	II (paddle)	100	Phosphate buffer, pH 7.4	900
Famotidine	II (paddle)	50	Phosphate buffer, pH 4.5	900
Azithromycin	II (paddle)	50	Phosphate buffer, pH 6.0	900

drugs with doses of 30 mg, 60 mg, 100 mg, 150 mg and 200 mg. The dose increased with certain interval in the range of 30–200 (mg) and drug selections conformed to the doses of commercial extended release tablets. Five ternary-component diagrams were drawn through a large number of experiments and five optimal formulation regions were obtained.

2.7. Cutting of the five optimal formulation regions

According to our principles of I: the cut-out region must be in the optimal formulation region; and II: the cut-out area must be the largest, the five optimal formulation regions were cut into parallelograms as large as possible. Two sides of the parallelogram ran parallel with the drug percentage line in the ternary-component diagram; the other two sides ran parallel to the NaCl percentage line. This process had the optimal formulation regions cut into the same shape in the same direction for the convenience of following equation fitting. Water-insoluble drugs (strength low to high) dextromethorphan hydrobromide (30 mg), dextromethorphan hydrobromide (60 mg), acyclovir (100 mg), actarit (150 mg) and acyclovir (200 mg) were chosen as validation drugs (drug selections conform to the doses of commercial extended release tablets) to, respectively, replace the model drug at the same dose level. The formulations corresponding to the vertexes of the five parallelograms were selected, followed by tableting, coating and in vitro dissolution tests to investigate if these formulation points meet the evaluating conditions of MOPTs drug release performance. By doing this, the rationality of parallelogram cutting was verified.

2.8. Design of the formulation prediction system

Regarding the doses of five model drugs above (30 mg, 60 mg, 100 mg, 150 mg and 200 mg) as vertical coordinate, a triangular prism model was established using the five corresponding ternary-component diagrams as the cross-sections by MATLAB® R2008a software. With the corresponding vertex coordinates of every two adjacent parallelograms in the ternary-component diagrams, four optimal formulation equations were fitted to form a segment of optimal formulation channel. Finally four segments connected into a whole optimal formulation channel in the triangular prism model. When selecting values which were not 30, 60, 100, 150 or 200 (mg) in the range of 30–200 mg on the vertical coordinate, we could calculate the corresponding fixed point coordinates through the fitted equations with the method of interpolation algorithm to design parallelograms. Visually, the optimal formulation channel was intercepted a cross section at the corresponding position. This section was the optimal formulation region of MOPTs for this dose. Then the formulation prediction system for MOPTs (FPS 1.0) was programmed by MATLAB® R2008a software. When the information of some water-insoluble drug was entered including the dose, the optimal formulation region for preparation of MOPTs was immediately obtained.

2.9. Evaluation of the predictive ability of the system

We chose water-insoluble famotidine (40 mg) and azithromycin (125 mg) as evaluation drugs (drug selections conform to the doses of commercial extended release tablets) because their doses are within 30–200 (mg) and different with model drugs for avoidance of repetition. After entering the information of them, FPS 1.0 gave the optimal formulation regions of them in the ternary-component diagrams. Formulation points were randomly selected in the optimal formulation regions. If the dissolution test results met the evaluating conditions of MOPTs drug release performance, the predictive ability of the system was tentatively confirmed.

3. Results and discussions

3.1. Application of ternary-component diagram for MOPTs

The ternary-component diagram for MOPTs was originally brought forward in this research. The initial and important role of it is to become the element of model establishment and system design. Apart from this, it can be applied in many ways. Firstly, the ternary-component diagram for MOPTs is beneficial for industrial manufacturing. Proper formulations can be chosen in the center of the optimal formulation region so that even accidental weighing errors will not much affect the drug release behaviors. Secondly, formulations consisted of components with different proportions in the range of optimal formulation region may be optionally selected according to actual situation of corporation and the material cost will be lowered. Thirdly, according to the change of drug release behaviors at different formulation points in the diagrams, optimal formulations can be found easily so as to improve the efficiency of experiments.

3.2. Selection of the most suitable PEO for MOPTs of water-insoluble drugs

Choosing gliclazide as model drug and eight kinds of PEO (WSR N10, WSR N80, WSR N750, WSR N1105, WSR N12K, WSR N60K, WSR 301 as well as WSR 303) as suspending agents, we prepared MOPTs. Then we drew eight ternary-component diagrams (Fig. 1). It is obvious from the figures that the area of the optimal formulation region in the ternary-component diagram of WSR N12K is the largest. Therefore, WSR N12K was selected as the most suitable PEO for water-insoluble drug MOPTs for further study.

Based on the results of our preliminary experiments, the hydrating rate, inherent viscosity and swelling capacity of WSR N12K are moderate in PEO series. So the time lag is not obvious for the formulation comprised of N12K and gliclazide powder is sufficiently suspended with WSR N12K. The ultimate cumulative release is almost complete and the dissolution profile is liner. Therefore, the optimal formulation region is much larger. Some formulations are even more ideal ($r = 0.9965$ and ultimate cumu-

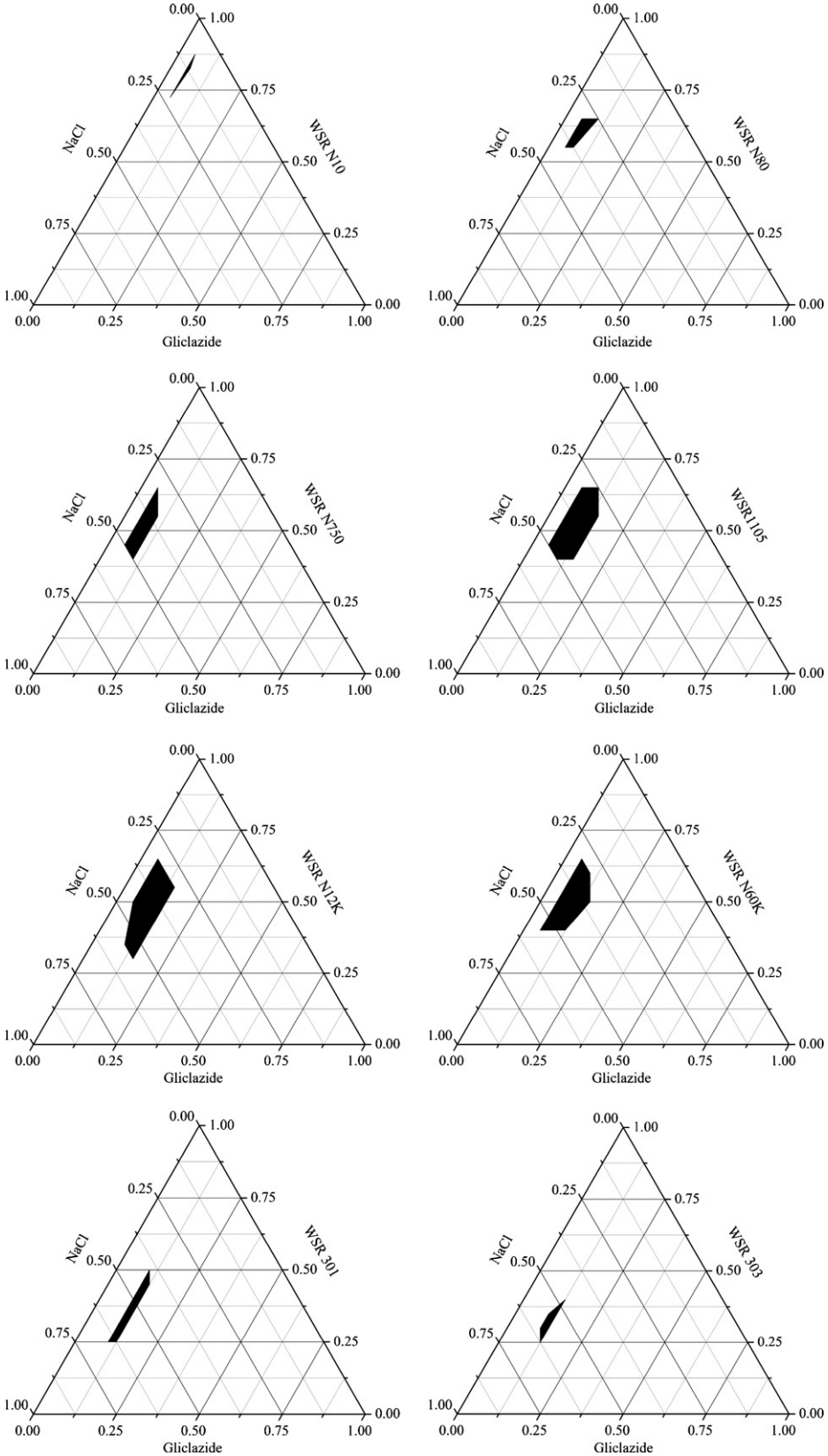

Fig. 1. Ternary-component diagrams using gliclazide as the model drug and WSR N10, WSR N80, WSR N750, WSR N1105, WSR N12K, WSR N60K, WSR 301 as well as WSR 303 as the suspending agents.

lative release = 99.00%, according to one of our data). So the MOPTs have the same effect as two-layer push–pull or three-layer osmotic pump tablets for gliclazide.

For the formulation comprised of lower M_w PEO, there is no time lag in release profile, but the period of drug delivery is shorter (8–10 h) and the cumulative release is not enough due to the high hydrating rate and low swelling capacity of PEO. The low inherent viscosity of PEO of lower M_w results in inadequate drug suspending. Therefore, the weight of core tablet should be increased, i.e. the content of PEO should be higher to suspend drug. For the formulation comprised of higher M_w PEO, obvious time lag (about 4 h) is seen in the release profile because the hydrating rate of PEO is quite low. Although the inherent viscosity and swelling capacity of higher M_w PEO increase a lot, these sorts of PEO are still suitable suspending agents for MOPTs. The drug release rate is zero-order after time lag and the cumulative release also meets the requirements. Therefore, higher M_w PEO can be applied to pulsatile MOPTs which perform controlled drug release a few hours after administration.

3.3. Preparation of ternary-component diagrams of five model drugs with different doses

Five ternary-component diagrams corresponding to the doses of 30 mg, 60 mg, 100 mg, 150 mg and 200 mg were drawn and five optimal formulation regions were obtained (Fig. 2). The figures illustrate that with the increase of drug dose from 30 mg to 200 mg, the area of the optimal formulation region decreases, which indicates that MOPTs are not very applicable to the drugs with higher doses. The figures also show that with the increasing drug dose, the optimal formulation regions change locations in the ternary-component diagram by a certain trajectory. This will provide a

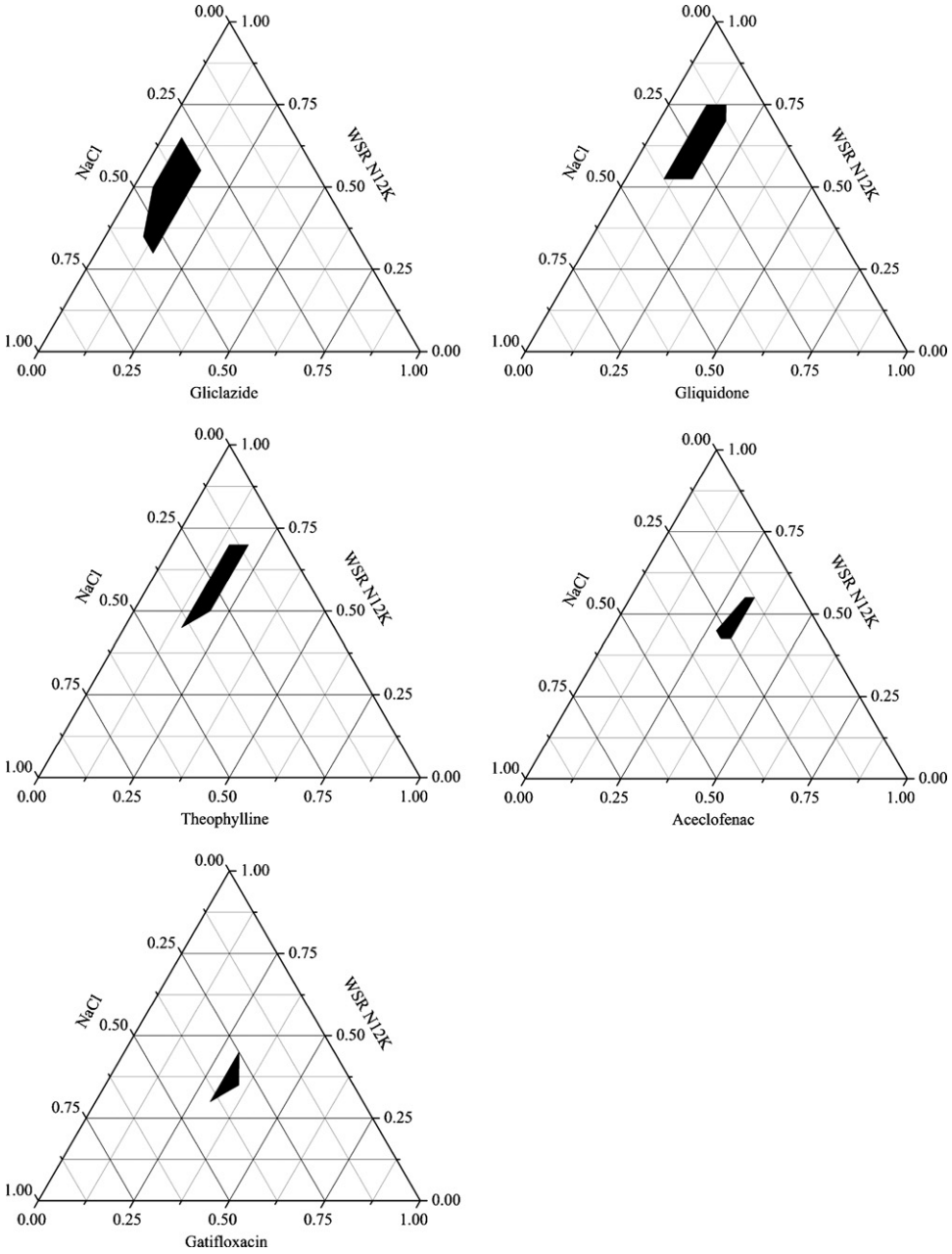

Fig. 2. Ternary-component diagrams using WSR N12K as suspending agent and gliclazide, gliquidone, theophylline, aceclofenac and gatifloxacin as model drugs with the doses of 30 mg, 60 mg, 100 mg, 150 mg and 200 mg, respectively.

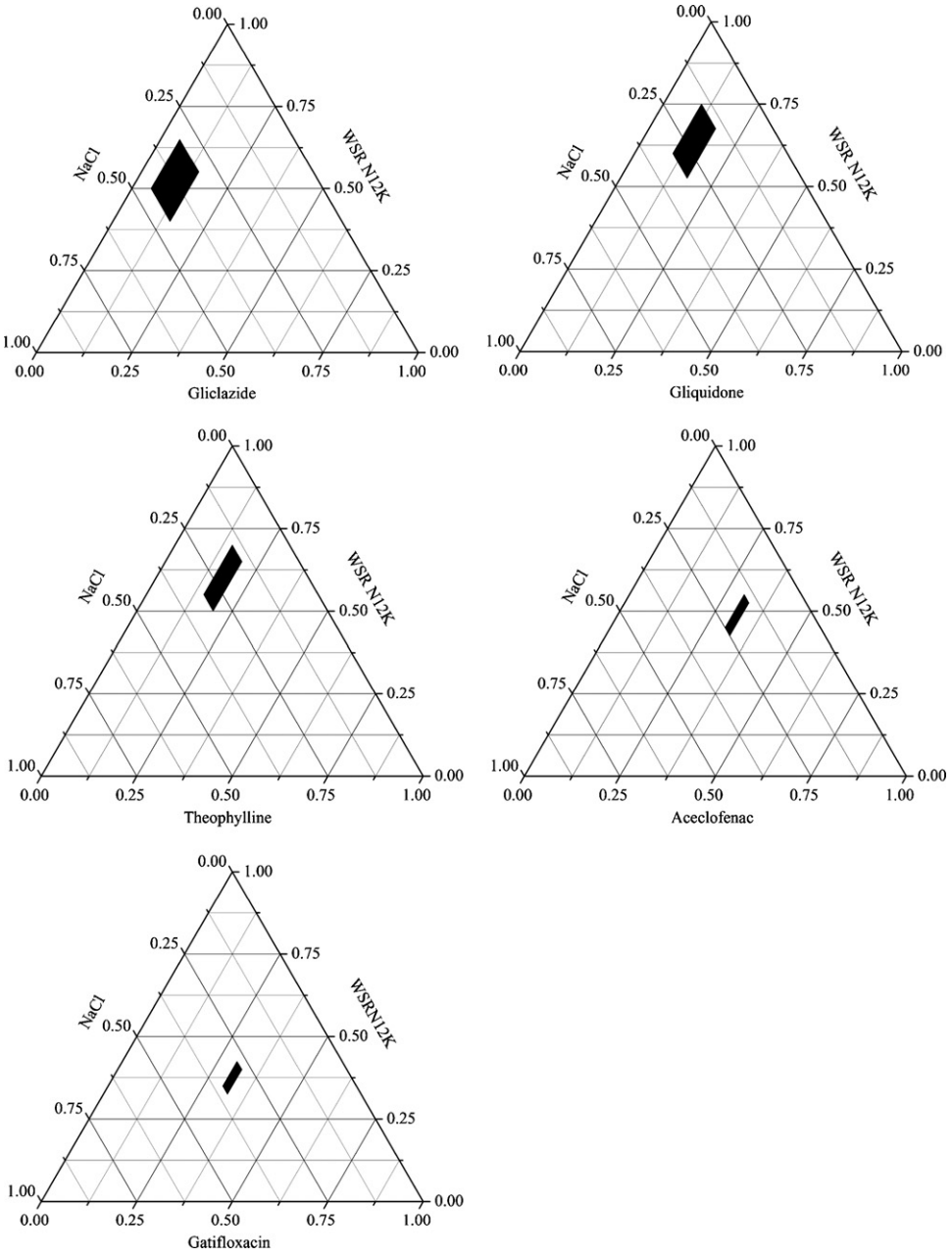

Fig. 3. Cutting parallelogram optimal formulation regions in the corresponding ternary-component diagrams with gliclazide, gliquidone, theophylline, aceclofenac and gatifloxacin as model drugs.

theoretical basis for establishing a spatial model and forming an optimal formulation channel in it.

3.4. Cutting of the five optimal formulation regions

Because the optimal formulation regions obtained above are in different shapes, we should cut them into the same shape in the same direction to facilitate the follow-up equation fitting. According to the cutting principles, the five optimal formulation regions were cut into parallelograms (Fig. 3) and the formulations corresponding to the vertexes of the five parallelograms were demonstrated in Table 2. Water-insoluble drugs dextromethorphan hydrobromide (30 mg), dextromethorphan hydrobromide (60 mg), acyclovir (100 mg), actarit (150 mg) and acyclovir (200 mg) were selected as validation drugs to verify the rationality of parallelogram cutting. In vitro dissolution test results for the vertex formulations of each parallelogram were also seen in Table 2. It is clear from the table that all these formulation points meet the evaluating conditions of MOPTs drug release performance, i.e. the cumulative release greater than or equal to 75%, the correlation coefficient of drug release profile greater than or equal to 0.99 and the period of drug delivery up to 10 or 12 h. Therefore, the cutting method to some degree is appropriate.

The cutting principle I—"the cut-out region must be in the optimal formulation region" means the cut-out region should be from the original optimal formulation region and the principle II—"the cut-out area must be the largest" means the cut-out region should include optimal formulations as many as possible. The cut-out parallelograms based on these principles are still optimal formulation regions for the five model drugs, but uncertain for other drugs. Therefore we choose validation drugs at the five dose levels to verify if the vertex formulations of each cut-out region are optimal formulations for the validation drugs. If so, the region cutting process has general significance.

Table 2
The formulations corresponding to the vertexes of the five parallelograms and the dissolution parameters of validation drugs for these formulation points.

Validation drug	Vertex formulation (percentage of drug, N12K and NaCl, respectively, %)	r	Cumulative release (%)	Period of drug delivery (h)
Dextromethorphan hydrobromide (30 mg)	(5, 65, 30)	0.9918	100.61	12
	(15, 55, 30)	0.9923	89.51	10
	(15, 40, 45)	0.9935	82.00	10
	(5, 50, 45)	0.9914	87.06	12
Dextromethorphan hydrobromide (60 mg)	(10, 75, 15)	0.9915	75.33	10
	(17.5, 67.5, 15)	0.9904	78.25	10
	(17.5, 52.5, 30)	0.9906	86.58	10
	(10, 60, 30)	0.9920	78.58	10
Acyclovir (100 mg)	(15, 70, 15)	0.9908	85.37	10
	(20, 65, 15)	0.9907	107.67	12
	(20, 50, 30)	0.9922	96.96	10
	(15, 55, 30)	0.9902	96.69	10
Actarit (150 mg)	(30, 55, 15)	0.9972	83.66	12
	(32.5, 52.5, 15)	0.9908	75.40	12
	(32.5, 42.5, 25)	0.9927	75.39	12
	(30, 45, 25)	0.9994	75.11	10
Acyclovir (200 mg)	(30, 42.5, 27.5)	0.9901	90.00	10
	(32.5, 40, 27.5)	0.9914	93.49	10
	(32.5, 32.5, 35)	0.9909	93.62	10
	(30, 35, 35)	0.9901	87.83	10

3.5. The establishment of the triangular prism model and the mechanism of interpolation algorithm

The triangular prism model and an optimal formulation channel in it were established by MATLAB® R2008a software. Fig. 4(A) and (B) shows the triangular prism model and the optimal formulation channel at different angles. The vertical coordinate of this triangular prism represents dose from 0 to 200 (mg). The whole triangular prism is formed by superposition of numerous ternary-component diagrams corresponding to dose from 0 to 200 (mg). Five blue parallelogram optimal formulation regions, correspond to the doses of 30, 60, 100, 150 and 200 (mg). With the vertex coordinates of every two adjacent parallelograms, four optimal formulation equations are fitted to form a segment of optimal formulation channel. Four segments, i.e. 16 equations connect into the whole optimal formulation channel in the triangular prism model. Because of privacy considerations, the equations are not disclosed. When we select a value in the range of 30–200 mg on the vertical coordinate, the triangular prism model will be inserted by a ternary-component diagram at the corresponding position. The interface of this ternary-component diagram and the optimal formulation channel will be the optimal formulation region of MOPTs for this dose (the yellow region in of Fig. 4(C)).

After the establishment of triangular prism model, the region corresponding to certain drug dose value can be expressed by a matrix comprised of four points (Takehiro and Yuichi, 2006), which can be represented by Eq. (1):

$$D^h = [p_1, p_2, p_3, p_4] = [(x_1, y_1), (x_2, y_2), (x_3, y_3), (x_4, y_4)] = [(u_1, v_1, w_1), (u_2, v_2, w_2), (u_3, v_3, w_3), (u_4, v_4, w_4)] \quad (1)$$

where h represents drug dose dereferencing [30,60, 100, 150, 200]; and p_{1-4} is the fixed points of the quadrangle after arrangement. According to different coordinate systems, rectangular coordinate is in the form of (x, y) and triangular coordinate is in the form of (u, v, w). If the actual data is not exactly equal to the values of h, linear interpolation method can be used to calculate the corresponding fixed point coordinates at any h value, so as to construct the polygon there. This can be briefly indicated by Eq. (2):

$$D^h = D^i \frac{h - h_i}{h_{i+1} - h_i} + D^{i+1} \frac{h - h_i}{h_i - h_{i+1}} \quad (2)$$

where h is given drug dose ($h_i \le h \le h_{i+1}$). Suppose the experimental data is as follows: drug dose = 45 mg, x = 30%, y = 50% (if triangular coordinate is used, the third value must be 100% − x − y = 20%), then the calculation process can be shown as Eq. (3) followed by

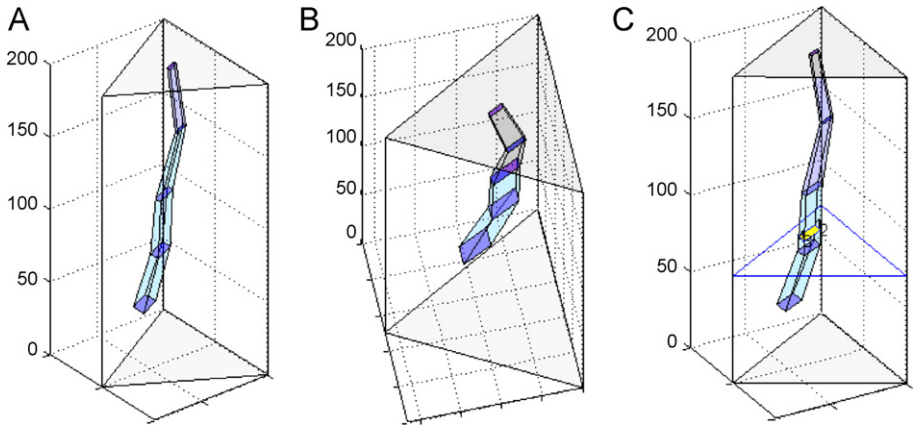

Fig. 4. The triangular prism model and optimal formulation channel.

determining if (x, y) is inside the polygon $D^{(45)}$:

$$\begin{cases} x_i^{45} = x_i^{30}\dfrac{45-30}{60-30} + x_i^{60}\dfrac{45-60}{30-60} \\ y_i^{45} = y_i^{30}\dfrac{45-30}{60-30} + x_y^{60}\dfrac{45-60}{30-60} \end{cases} \quad (3)$$

3.6. Design of the formulation prediction system

MATLAB® R2008a was used for programming of formulation prediction system. Because of privacy considerations, the programming code is not disclosed. Fig. 5(A) shows the welcome window. The software package is named as FPS (acronyms of "formulation prediction system") with the version of 1.0. Fig. 5(B) indicates the operation window which is composed of four parts. The top part is button region. When the "Drug data" button is clicked, a window will pop up (Fig. 5 (C)) which allows inputting drug information, including name and dose (mg/tablet), and selecting drug solubility as well as controlled delivery time. According to USP31-NF26, drug solubility is categorized into two major types: water-soluble drugs (including very soluble, freely soluble and soluble) with the solubility ≥1/30 g/ml, and water-insoluble drugs (including sparingly soluble, slightly soluble, very slightly soluble and practically insoluble) with the solubility ≤1/30 g/ml. The controlled delivery

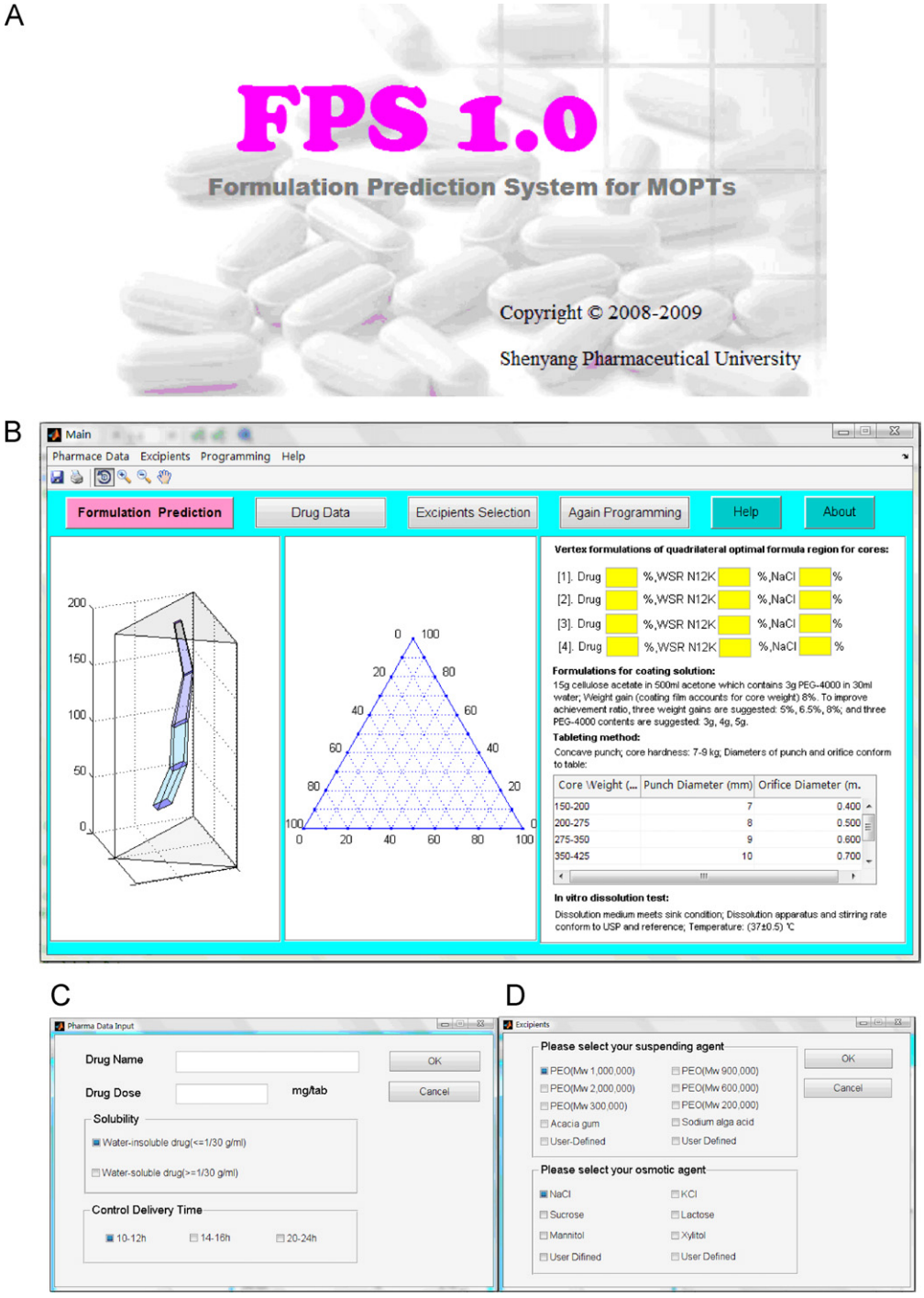

Fig. 5. Windows in FPS 1.0.

time is divided into 10–12 h, 14–16 h and 20–24 h based on the drug elimination half-life after a single dose. As far as the current study is concerned, only the options of "water-insoluble drug" and "10–12 h" are available. When the "Excipients selection" button is clicked, another window will pop up (Fig. 5 (D)) for the selections of suspending agent and osmotic agent for core tablets. Acacia gum and sodium alga acid are selected as suspending agent options based on the references (Lu et al., 2003; Alf et al., 2007; Güngör et al., 2003; Barclay et al., 1990; Ayer et al., 1990). The osmotic agents are all soluble micromolecular salts, saccharides and alcohols. "User defined" is for other suspending and osmotic agents in again programming. Up to now just the options of "PEO (M_w 1,000,000)" (N12K) and "NaCl" are selectable. The "Formulation Prediction" button is the execution button. After it is clicked, the prediction results will be shown in the three regions below. The left part is the result demonstration region through triangular prism model. When the "Formulation Prediction" button is executed, the triangular prism model will be inserted by a ternary-component diagram at the corresponding position to three-dimensionally display the optimal formulation region for this dose (Fig. 4(C)). The middle part is the result demonstration region through ternary-component diagram. The yellow part represents the parallelogram optimal formulation region. The right part demonstrates the results and data including the vertex formulations of optimal formulation region, coating solution formulation, tableting and in vitro dissolution test methods. To achieve the target as soon as possible, three weight gains are suggested: 5%, 6.5% and 8%; and three PEG-4000 contents are suggested: 3 g, 4 g and 5 g according to our previous studies, which show that higher weight gain will bring about better linearity of the drug release profile, and higher PEG-4000 content

Table 3
Corresponding relationship between tablet core weight and punch diameter.

Core weight (mg)	Punch diameter (mm)	Orifice diameter (mm)
150–200	7	0.4
200–275	8	0.5
275–350	9	0.6
350–425	10	0.7
425–550	11	0.8
550–700	12	0.9

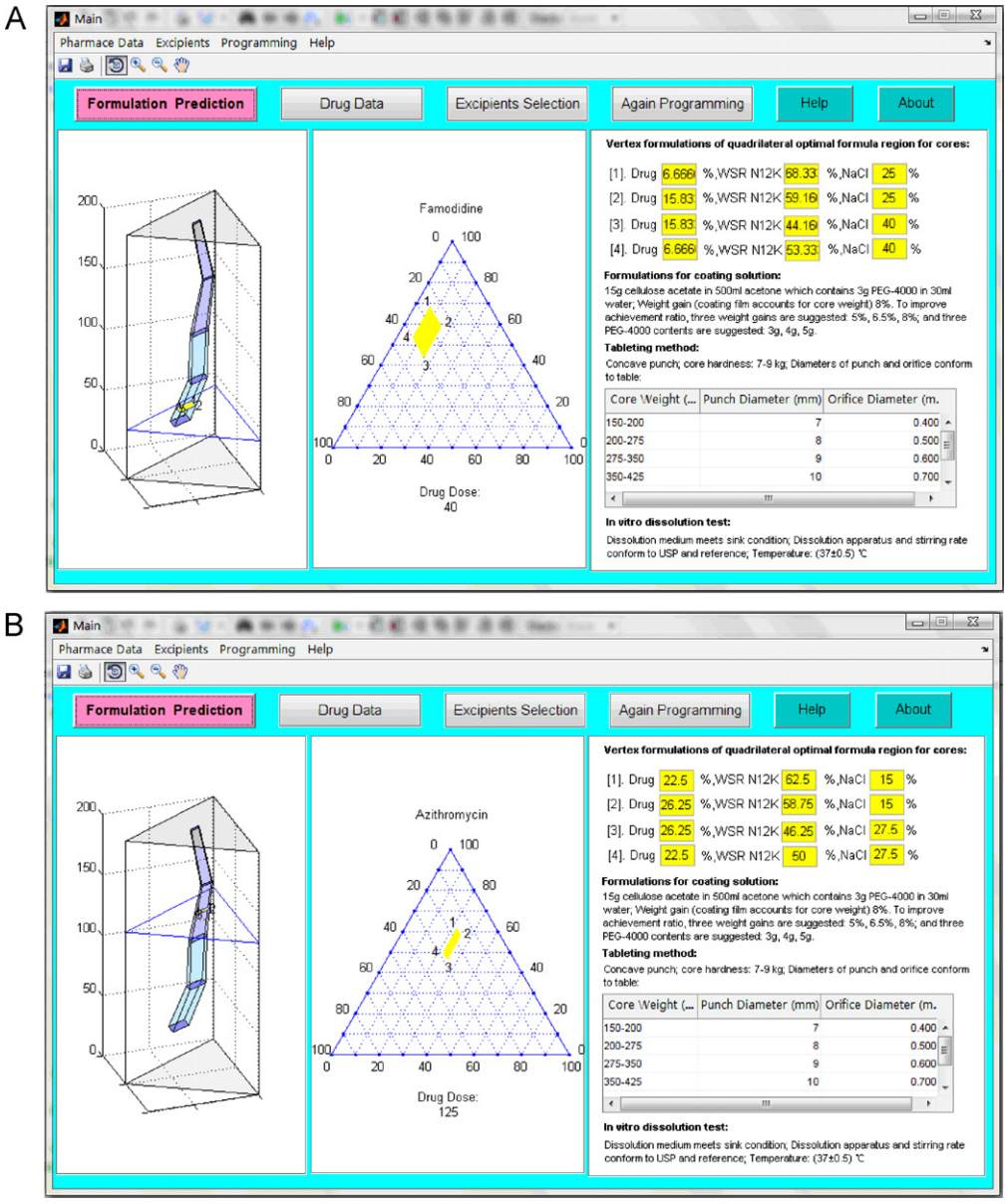

Fig. 6. The prediction results for famotidine and azithromycin.

Table 4
The dissolution test results of four randomly selected formulations.

Validation drugs	Formulation no.	Percentage of drug, N12K and NaCl, respectively, (%)	*r*	Cumulative release (%)	Period of drug delivery (h)
Famotidine	Formulation 1	15, 55, 30	0.9933	91.65	10
	Formulation 2	6.67, 60, 33.33	0.9900	95.03	12
Azithromycin	Formulation 3	23, 50, 27	0.9941	81.35	12
	Formulation 4	26, 55, 19	0.9968	76.04	10

will result in higher ultimate cumulative release. The corresponding relationship between tablet core weight and punch diameter is indicated in Table 3.

3.7. Evaluation of the predictive ability of the system

Water-insoluble drugs famotidine and azithromycin were chosen as evaluation drugs. The prediction results are seen in (A) and (B), respectively, in Fig. 6. We randomly chose four formulations in these two optimal formulation regions. The dissolution test results and dissolution profiles are shown in Table 4 and Fig. 7, respectively. The results of the four randomly selected formulations for two doses all satisfy the evaluating conditions of MOPTs drug release performance. Therefore, the predictive ability of the system is tentatively confirmed and the experiment efficiency is greatly improved.

Compared with other statistical prediction and optimization systems for the same application, this formulation prediction system has some advantages. For one thing, it is convenient and efficient. All the information we need to provide is drug name and daily dose. After we input the information, the system will give us optimal formulations in seconds without artificial calculation. For another, what this system predicts is an optimal formulation region rather than a single formulation. Therefore, we can either choose proper formulation in the center of the region to eliminate bad effect caused by accidental weighing errors, or select other formulations according to material cost and actual situation of corporation.

Some limitations for this formulation prediction system are worth paying attention. Firstly, this system is only suitable for drugs with dose from 30 mg to 200 mg. If the dose is too low, the optimal formulation region cannot be appropriately drawn in the ternary-component diagram; if the dose is over high, the drug is not suitable to be prepared into MOPTs. Secondly, the system is now just available for water-insoluble drugs and core excipients selections are confined to WSR N12K and NaCl. Hence more and more core excipients data remains to be further studied and input during the process of software again programming. Thirdly, only in vitro dissolution was used to test formations, rather than in vivo testing. Therefore the validity of system for in vivo situation needs to be verified. Fourthly, for actual development of formulation for commercial use, addition of glidant, lubricant, filler and binder is inevitable. Effects of these important excipients on the release pattern should be included for further developing predictive software.

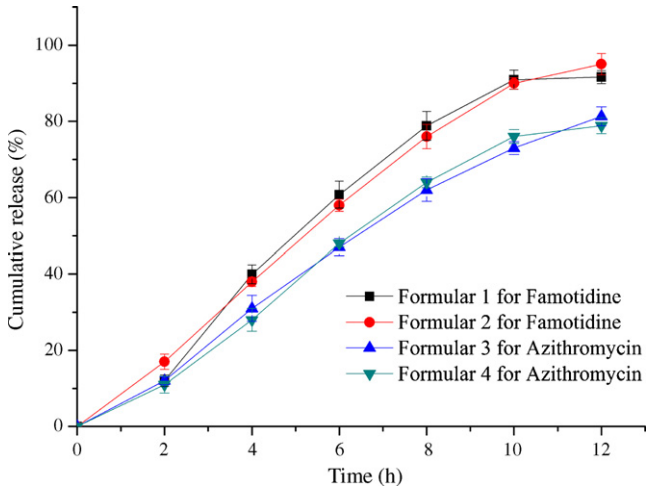

Fig. 7. The dissolution profiles of four randomly selected formulations (avg., $n = 6$).

4. Conclusions

Ternary-component diagram was brought forward to evaluate MOPTs formulations. According to evaluating conditions, the optimal formulation regions were delimited in ternary-component diagrams. WSR N12K was selected as the most suitable PEO for preparing water-insoluble drug MOPTs. Using WSR N12K as suspending agent and gliclazide, gliquidone, theophylline, aceclofenac as well as gatifloxacin as model drugs, we drew five ternary-component diagrams, which were then cut into parallelograms. Dextromethorphan hydrobromide, acyclovir and actarit were selected as validation drugs and the rationality of parallelogram cutting was verified. A triangular prism model was established and the formulation prediction system was designed by MATLAB® software. After entering information of some water-insoluble drug and selecting excipients, we immediately obtained the optimal formulation region for preparing MOPTs with the method of interpolation algorithm. Famotidine and azithromycin were chosen as evaluation drugs. The results of the four randomly selected formulations all satisfied the evaluating conditions of MOPTs drug release performance. Therefore, the predictive ability of the system was tentatively confirmed and the experiment efficiency was greatly improved. Some limitations for this system are worth paying attention: this system is only suitable for drugs with dose from 30 mg to 200 mg; more and more excipients data remain to be further studied and input during the process of software again programming; and the validity of system for in vivo situation needs to be verified.

Acknowledgements

We acknowledge Rongwu Xiang for his continued support for work in the area of computer model design and Xiangdong Su for his help in software programming.

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