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Design of an expert system for the development and formulation of push–pull osmotic pump tablets containing poorly water-soluble drugs

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ABSTRACT

The purpose of this article was to build an expert system for the development and formulation of push–pull osmotic pump tablets (PPOP). Hundreds of PPOP formulations were studied according to different poorly water-soluble drugs and pharmaceutical acceptable excipients. The knowledge base including database and rule base was built based on the reported results of hundreds of PPOP formulations containing different poorly water-soluble drugs and pharmaceutical excipients and the experiences available from other researchers. The prediction model of release behavior was built using back propagation (BP) neural network, which is good at nonlinear mapping and learning function. Formulation design model was established based on the prediction model of release behavior, which was the nucleus of the inference engine. Finally, the expert system program was constructed by VB.NET associating with SQL Server. Expert system is one of the most popular aspects in artificial intelligence. To date there is no expert system available for the formulation of controlled release dosage forms yet. Moreover, osmotic pump technology (OPT) is gradually getting consummate all over the world. It is meaningful to apply expert system on OPT. Famotidine, a water insoluble drug was chosen as the model drug to validate the applicability of the developed expert system.

1. Introduction

In recent years, there has been a sharply increasing interest in the development of oral osmotic pump tablets (OPT). Osmotic pump is a drug delivery system that utilizes osmosis to drive drugs out, which can delivery drug at a constant rate. Various types of oral osmotic pumps have been developed and studied to deliver drugs possessing different aqueous solubility. In the 1970s, elementary osmotic pump (EOP) (Theeuwes and Higuchi, 1972; Theeuwes, 1975) was developed. As known to all, drugs with moderate water solubility are easy to make into EOP. Another kind of osmotic pump was porosity osmotic pump, which was suitable for the delivery of water-soluble drugs (Verma et al., 2000). Osmotic pump of this kind has leachable water-soluble components in its membrane, thus delivery orifice is formed in situ when the water-soluble components dissolve.

For poorly water-soluble drugs, since they could hardly be dissolved in water, they could not produce osmotic pressure by themselves. Many effective ways were tried to increase drug solubility for improving the drug release. For example, convert active pharmaceutical ingredients (API) into ionic substance by reacting with or adding alkali/acid (Lu et al., 2002; Ouyang et al., 2005); use (SBE) 7m-β-CD as a solubilizer (Okimoto et al., 1999, 2004). It is ideal for water-insoluble drug to release in the form of suspension. For example, Polyethylene oxide (PEO) (Liu et al., 2000) was used as a suspending and osmotic agent to prepare nifedipine monolithic osmotic tablet system (MOTS). However, if the viscosity inside the system was not proper, drug sedimentation might happen which would revoke incomplete drug release. Thus, although researchers had put some effort to develop monolithic osmotic pumps for water-insoluble drugs, the push–pull osmotic pump (PPOP) which was presented by Theeuwes in 1970s (Theeuwes, 1978) is still the most practical way to prepare the water-insoluble drugs into osmotic pump system. And most of the commercially available osmotic pump products containing water-insoluble drugs are of this kind, for example nifedipine push pull osmotic pump (Procardia XL®, Pfizer and Adalat®, Bayer) and glipizide push pull osmotic pump (Glucotrol®, Pfizer).

Expert system is one of the most popular subjects in artificial intelligence domain. An expert system is a knowledge-based

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system that draws upon the knowledge of human experts captured in a knowledge base and then emulates experts' thought to solve problems in the selected domains (Cai and Xu, 2004; Rowe and Roberts, 1998). Generally, most expert systems have three major components: a man–machine interface, a knowledge base in which all foregone knowledge pertaining to the selected domain is stored and an inference engine that could use the stored knowledge to manipulate relevant problems. Expert systems can either be developed using conventional computer languages/special purpose languages or developed shells/toolkits. Conventional languages such as PASCAL, Basic and C have the advantages of wide applicability and full flexibility to create the control and inference strategies.

Bradshaw published the first report referenced to the use of expert systems in pharmaceutical product formulations on 27 April 1989 in the London *Financial Times* (Rowe and Roberts, 1998). Since then, several companies and academic institutes reported their experiences in this area (Table 1, Aguilar et al., 2009; Aleksander and Renata, 2007; Batrman et al., 1996; Cai and Xu, 2004; Lai et al., 1996; Perez et al., 2006; Rowe, 1993; Rowe et al., 1995, 1998; Yannis, 1998).

Since the technology of PPOP is gradually getting popular, developing an expert system that is able to create PPOP formulations with little or no human intervention would be a valuable and meaningful subject. The objective of this study was to design an expert system for the development and formulation of push–pull osmotic pump tablets containing poorly water-soluble drugs, which was named ESFppop, to shorten the developing period of push–pull osmotic pump tablets. Hundreds of PPOP formulations were studied according to different poorly water-soluble drugs and pharmaceutical acceptable excipients. The regularity of formulation components and manufacture procedures was summarized from the original experimental data and then the database was built. Rule base of the system was built mainly based on the original experimental data and the experiences obtained by other researchers. SQL Server was employed as database management system (DBMS). The prediction model of release behavior was built using BP neural network, which is good at high nonlinear mapping and learning function. Formulation design model was built based on the prediction model of release behavior, which was the nucleus of the inference engine. Man–machine interface was designed using VB.NET. Finally, water insoluble drug famotidine was chosen and ESFppop was applied to design the PPOP formulations. It could be considered that ESFppop was practicable according to the results.

2. Materials and methods

2.1. Materials

Poorly water-soluble drugs indapamide (purchased from Beijing Yanjing pharmaceutical plant, Beijing, China), gliclazide (purchased from Shandong medicine industry graduate school system pharmaceutical factory, Shandong, China), dipyridamole (gifted samples from Shenyang No. 1 Pharmaceutical Factory, Liaoning, China), famotidine (Yaodayaoye Ltd. Shenyang China), et al., were employed as models. Polyethylene oxides (PEOs, PEO WSR N∼10, PEO WSR N∼80, PEO WSR N∼750, PEO WSR N∼3000, PEO WSR 205, PEO WSR 1105, PEO WSR N∼12K, PEO WSR N∼60K, PEO WSR301, PEO WSR Coagulant, PEO WSR303) were gifted from Dow Chemical (New Jersey, USA). Hydroxy-propyl methyl celluloses (HPMCs, HPMC K4M, HPMC K15M, HPMC K100M) were supplied by Shanghai Colorcon Coating Technology Ltd. (Shanghai, China) for free. Polyvinyl pyrrolidones (PVPs, PVP K30, PVP K90, and PVP S630) were a gift from International Specialty Products (ISP) Company (New Jersey, USA). Cellulose acetate (CA, 54.5–56.0 wt.% acetyl content) was obtained from Shanghai Chemical (Shanghai, China). Polyethylene glycols (PEGs, PEG800, PEG2000, PEG4000, PEG6000)

Table 1
Published applications of pharmaceutical product-formulation expert systems.

Company/Institution (system name)	Domain	Developed/first reported year
University of Heidelberg (Galenical Development System)	Aerosols, capsules, tablets, IV injections	1990
Boots Company	Topicals	1990
Cadila Laboratories	Tablets	1992
Zeneca Pharmaceuticals	Tablets/parenterals/ film coatings	1993/1995/1998
University of London/Capsugal	Capsules	1996
Sanofi Research	Capsules	1996
University of London	Liposomes	1998
University of Barcelona (SeDeM Diagram)	Capsules, tablets, suspension	2006

Table 2
The aspects studied in PPOP formulation and preparation procedures.

Aspects	Levels of aspects studied	
	Component categories	Amount level
Tablet core		
Drug layer		
API	Indapamide, gliclazide, dipyridamole, et al.	1.5–200 mg
Suspension agent	PEOs (Mol. Wt. 100,000–1,000,000), HPMCs	0.8–200 times of API (w/w)
Osmotic agent	NaCl, KCl, glucose, xylitol and et al.	0–10% of drug layer (w/w)
Binder	PVPs	0–10% of drug layer (w/w)
Push layer		
Extender	PEOs (Mol. Wt. 200,000–6,000,000)	10–100% of drug layer (w/w)
Osmotic agent	NaCl, KCl, glucose, xylitol and et al.	0–50% of extender (w/w)
Binder	PVPs	0–10% of push layer (w/w)
Pigment	Ferric oxide	1–4% of push layer (w/w)
Coating		
Pore former	PEGs, NaCl, KCl, glucose, xylitol, PVPs	0–40% of CA (w/w)
Weight gain	0–20% of tablet core (w/w)	
Orifice diameters	0.4–1.2 mm	
Core hardness	4–16 kg/cm^2	
Granulate	Yes/no	
Orifice position	Drug layer	Both layers

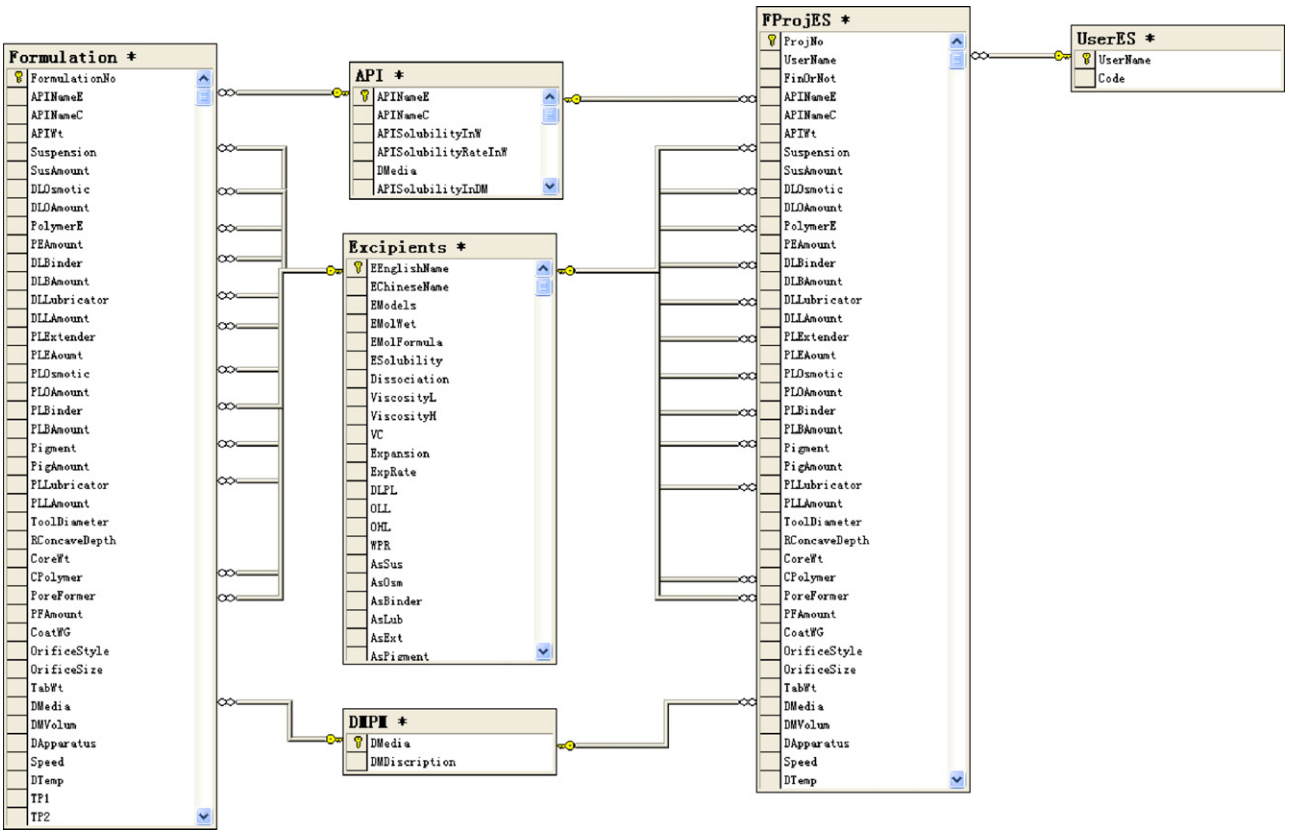

Fig. 1. Relations of tables in the database. Formulation*: the table records the foregone formulations and their dissolution results; API*: the table records the information of active pharmaceutical ingredients; Excipients*: the table records the information of excipients; DMPM*: the table records the dissolution media and preparation methods; FprojES*: the table records the information of designed formulation and projects; UserES*: the table records username and login codes.

were bought from Pudong Gaonan Chemical (Shanghai, China). All other chemicals were of analytical grade. ThinkPad T61, Windows XP professional, VB.NET and SQL Server 2000 were also used.

2.2. Methods

2.2.1. Formulation and manufacture procedure study

As known to all, the general structure of PPOP mainly contains the semi-permeable coating film and the tablet core which includes the drug layer and push layer. Drug layer is composed of API, suspension agent, osmotic agent, binder and lubricator. The ingredients in push layer are extender, osmotic agent, binder, pigment, lubricator. Cellulose acetate is commonly used as the coating material, while the pore former is used in the coating film to adjust the velocity of water permeation. Each component that may influence PPOP drug release and every step of the procedure were studied (Table 2).

Dissolution tests were performed according to the dissolution methods in USP30 and CP2005. The solubility and solution rate of the API in different media were tested. The viscosities, water uptake abilities, water uptake rates, swelling indexes and swelling rates of PEOs were also studied. Some other information such as molecu-

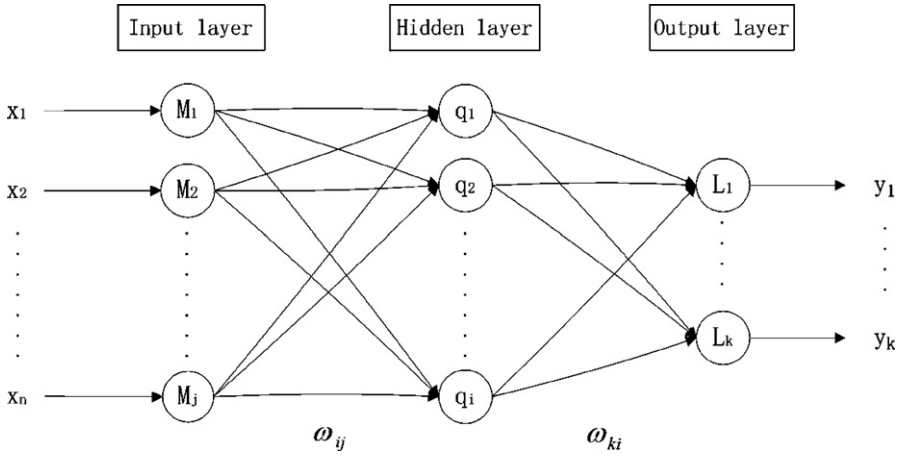

Fig. 2. Structure of BP neural networks. $x_1 \ldots x_n$: input data; $M_1 \ldots M_j$: neurons of input layer; $q_1 \ldots q_i$: neurons of hidden layer; $L_1 \ldots L_k$: neurons of output layer; $y_1 \ldots y_k$: output data; ω_{ij}: weighting coefficients between the neurons of input layer and hidden layer; ω_{ki}: weighting coefficients between the neurons of output layer and hidden layer.

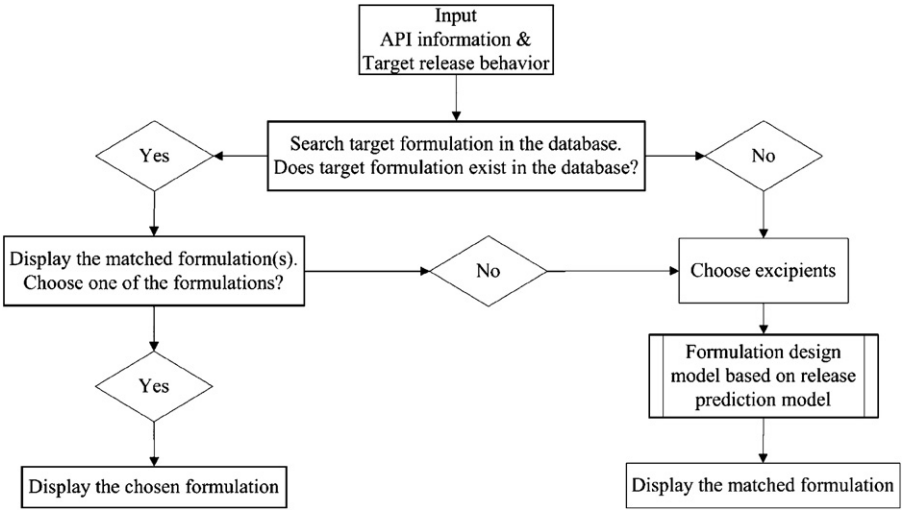

Fig. 3. The formulation design workflow of the expert system.

lar weight (Mol. Wt.), structure et al. was obtained from literatures such as the certificate of analysis. After all the data were gained, the relationship between the formulation/procedures and dissolution behaviors was studied. Then the regularities of formulation components and manufacture procedures were summarized.

2.2.2. The construction of rule base

The rule base was composed of a series of rules that could set the operational scopes and requirements of the system and the inference engine thread. The rules were established from the regularities of formulation/manufacture procedure studies and the experience from PPOP professors. Some of the rules were static, which were saved in the database; while the others were dynamic, which were planted in the inference engine, such as procedures. Details of rules could refer to the literature (Zhang et al., 2009).

2.2.3. The construction of database

SQL Server 2000 was employed to build and manage the database. Tables that used to record the information of API/excipients, dissolution methods, formulations, dissolution

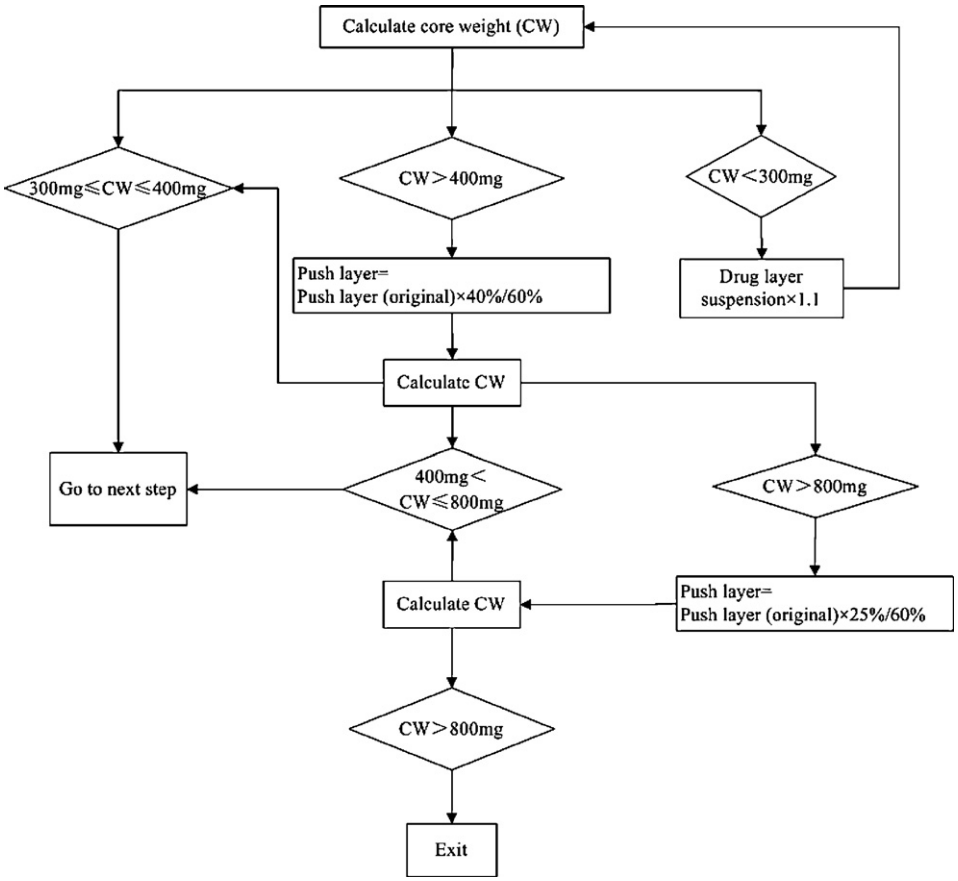

Fig. 4. Workflow of core weight modification (auto). Exit: The system cannot get an acceptable result, then exits the processes and informs the user. Go to next step: The system get an acceptable result, and then move to next step.

results, projects' information, et al., were designed. The relations between different tables were built and the synchronization was set (Fig. 1). The data filled into the database came from the formulation/manufacture procedure studies and the messages input by users when the system was applied.

2.2.4. The design of the prediction model of release behavior

The prediction model of release behavior was designed based on BP artificial neural networks (ANN), the structure of the ANN was displayed in Fig. 2. The model first learned from the data in the database and then could do the prediction.

2.2.5. The design of formulation design model and the accomplishment of inference engine

Three steps were designed in the formulation design model. First step, set the initiate formulation according to the related rules in rule base; second step, adjust the tablet core weight according to the initiate formulation and related rules in rule base; third step, adjust the formulation according to the prediction model of release behavior. Besides the formulation design model, the inference engine contained a search model, which could search the request formulation according to the input information in the database if the formulation had already been recorded in the database.

2.2.6. The design of man–machine interface

The man–machine interface was designed using VB.NET program, which is an object-oriented program. The man–machine interface accomplished to associating the database and the inference engine.

2.2.7. The first try of the designed system

Water insoluble drug famotidine was chosen as a test drug and expert system built in the study was applied to design the PPOP formulations. First, input the information that the system needed and run the program. Then the system displayed the potential target formulations. The sample products of the potential target formulations were prepared and tested to validate if the real target formulation was found.

3. Results and discussions

3.1. The designed expert system

The workflow of the main part of the expert system was displayed in Fig. 3. First, the system should receive the necessary information including API information and the target release behavior. The API information included the solubility and solution rate in water and dissolution media, dosage, et al. The target release behavior referred to dissolution media, controlled release time, et al. After that, the system would search the possible formulations in the database (saved formulations) according to the received information. If no matched formulation could be found in the database or the formulations found in the database were not accepted by the user, the system then run the formulation design model.

Formulation design model, which was the nucleus of the inference engine, was built based on the prediction model of release behavior, database and rule base. The first step was initializing the formulation according to the rule base, then modifying the tablet core weight into a reasonable range (Figs. 4 and 5), finally modifying the formulation to match the target release behavior (Fig. 6).

Fig. 5. Workflow of core weight modification (selected core weight limit). Exit: The system cannot get an acceptable result, then exits the processes and informs the user. Go to next step: The system get an acceptable result, and then move to next step.

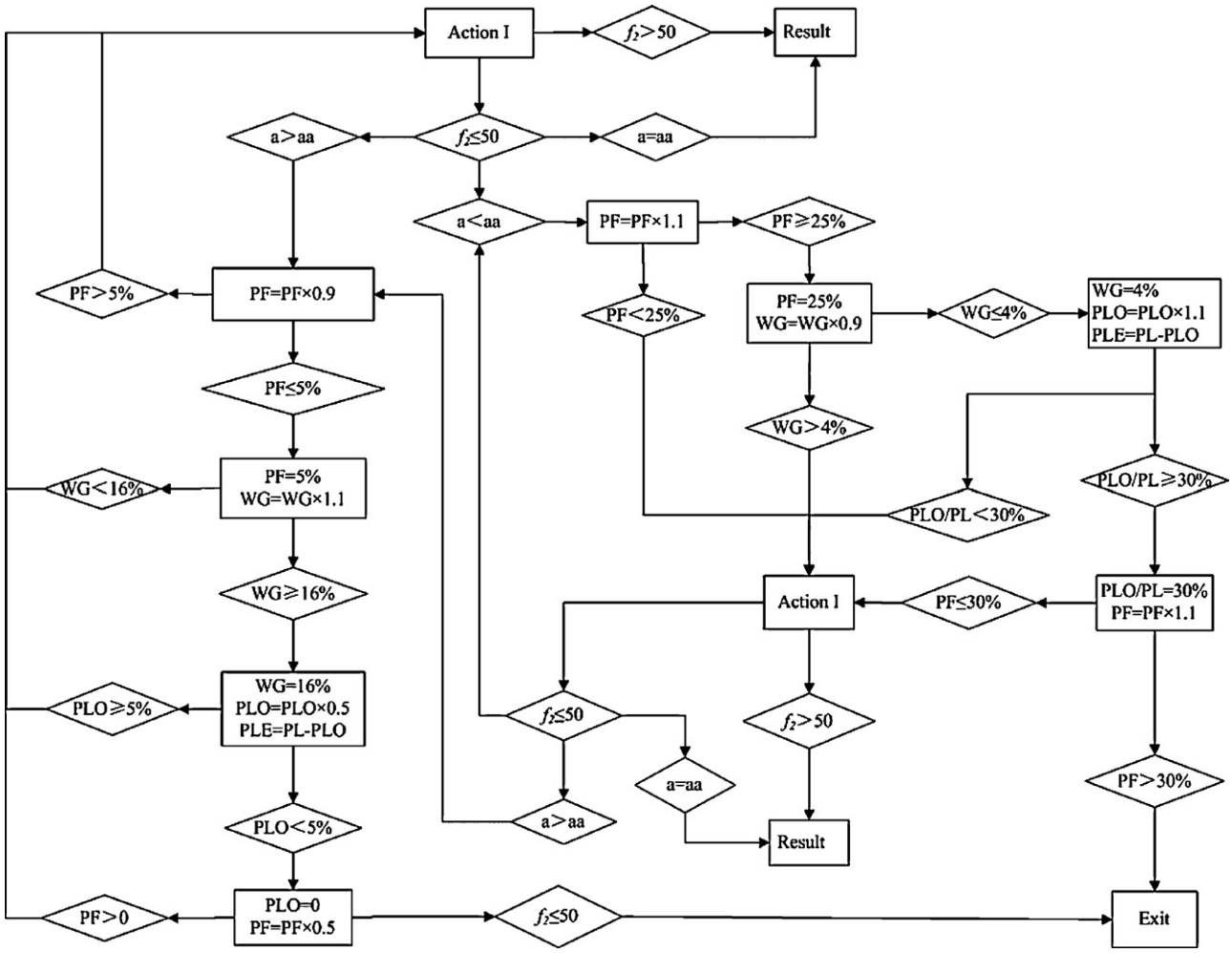

Fig. 6. Workflow of formulation modification. Action I: Predict drug release using prediction model and calculate the f_2 between the dissolution profile of designed formulation and the target dissolution profile; PLO: the quality of osmotic agent used in push layer; PLE: the quality of extender used in push layer; PL: the quality of push layer; WG: coating weight gain; PF: the percentage of pore former used in the coating; a: release rate of designed formulation; aa: target release rate; Exit: The system cannot get an acceptable result, then exits the processes and informs the user.

f_2 is the similarity factor suggested by FDA. The f_2 factor can be calculated as follows (Shah et al., 1998):

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-(1/2)} \times 100 \right\}$$

where R_t and T_t stand for the dissolution value at time t of the reference batch (traditional PPOP) and the test batch (novel PPOP), respectively; n is the number of time points. If the similar factor (f_2) is not less than 50, the two drug release profiles are considered to be similar.

Table 3
Formulation design results of the expert system.

Component	Formulation I	Formulation II	Formulation III
Tablet core			
Drug layer			
Famotidine	40 mg ml^{-1}	40 mg ml^{-1}	40 mg ml^{-1}
PEO WSR N~80	160 mg ml^{-1}	160 mg ml^{-1}	160 mg ml^{-1}
Magnesium stearate	1 mg ml^{-1}	1 mg ml^{-1}	1 mg ml^{-1}
Push layer			
PEO WSR coagulant	121 mg ml^{-1}	121 mg ml^{-1}	121 mg ml^{-1}
Magnesium stearate	0.6 mg ml^{-1}	0.6 mg ml^{-1}	0.6 mg ml^{-1}
Coating solution			
CA	28.5 g	28.5 g	28.5 g
PEG4000	1.5 g	1.5 g	1.5 g
Acetone	1000 ml	1000 ml	1000 ml
Water	15 ml	15 ml	15 ml
Coating weight gain	10%	12%	15%
Tooling diameter	9 mm	9 mm	9 mm
Orifice	0.6 mm	0.6 mm	0.6 mm

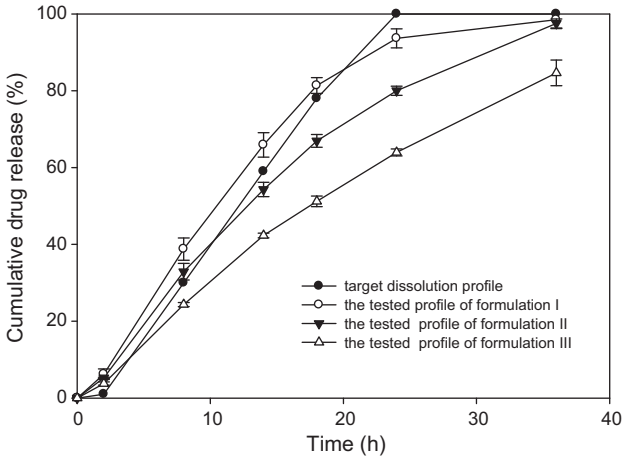

Fig. 7. Dissolution release profile of the designed formulations and the predicted dissolution profile target formulation (USP apparatus II (with sinker), 37 ± 0.5 °C, 100 rpm, 900 ml pH 4.5 PBS, $n = 6$).

3.2. The first try of the designed system

Famotidine is one of the third generation H_2 receptor blocking agents, which is used to treat peptic ulcer of stomach and duodenum. It is meaningful to apply extended release dosage forms including osmotic pump tablets on famotidine whose half-life is about 3 h according to the literatures (Zhang et al., 2001; Chen et al., 2007).

It was planned to design a formulation that can release drug for 24 h. According to the necessary input data and the USP30 dissolution method, the solubility of famotidine in water (1.1 mg ml^{-1}) and the solution rate in dissolution media (2335 μg ml^{-1} min^{-1}, pH 4.5 phosphate buffer) were tested. After running the program, three formulations (Table 3) and the target dissolution profile (Fig. 7) were displayed. The three displayed formulations were almost the same except for the coating weight gain.

The PPOP products were prepared according to the designed formulations. The dissolution tests were carried out by using 900 ml of pH 4.5 potassium phosphate (pH 4.5 PBS) as the medium in USP paddle apparatus at 37 ± 0.5 °C, the stirring rate was 100 rpm (Chen et al., 2007). It was shown in Fig. 7 that the dissolution profile of Formulation I was similar to the target dissolution profile ($f_2 = 53$) which means that Formulation I could be accepted as the target formulation. Meanwhile, the results also revealed the disadvantage of the designed expert system. Deviation between the results and predictions obviously existed which might be caused by the insufficiency of the database. Nonetheless, the results indicated that the designed expert system could help people to find the target PPOP formulation in a very short period, which indicated that the expert system could shorten the PPOP developing period.

4. Conclusion

Poorly water-soluble drugs with extremely different dosages were employed and hundreds of PPOP formulations were studied. Regularities of formulation components and manufacture procedures were summarized, and then the database, rule base, prediction model of release behavior, formulation design model and man–machine interface were built. An expert system for the development and formulation of push–pull osmotic pump tablets containing poorly water-soluble drugs, ESFppop, was established. Water insoluble drug famotidine was chosen as the model drug and ESFppop was used to design the PPOP formulations. It was considered that ESFppop was applicable and the designed expert system could help people to find the target PPOP formulation in a very short period, which meant that ESFppop could shorten the PPOP developing cycle. According to the results and discussion, improvement of the expert system should still be carry out in the future work such as expanding the capacity of the database, adding new rules/modifying the rules when more experience and regularities are found by scientists.

This study was also expected to throw out a minnow to catch a whale, introduce more advanced technology into pharmaceutics, and dedicate our effort to a faster, better and greater development of pharmaceutical industry.

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