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Orignal Article

Preparation of Insoluble Matrix Tablets of Theacrine

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Authors contribution:

Sha Li and Rongrong He conceived the idea, designed and supervised the research. Zhen Zhang and Junming Lin performed the research, conducted the analysis and wrote the paper. Yani Tan contributed to data collection and analysis. All authors contributed to the writing and revisions.

Core tip:

Theacrine (1,3,7,9-tetramethyluric acid, TC) is a purine alkaloid abundantly presented in tender leaves of *Camellia assamica* var. *kucha Chang* et Wang, which had anti-inflammatory, analgesic and anti-depression effects. In this work, insoluble matrix tablets of TC were prepared to achieve sustained release by wet granulation tableting process. The results showed that insoluble matrix tablets of TC were prepared with ethyl cellulose (EC) as matrix material, and the tablets exerted good sustained release behaviour. The TC tablets were hopeful to provide a new preparation of prolonged action for treatment of depression and inflammation.

Abstract:

Background Theacrine (1,3,7,9-tetramethyluric acid, TC) is a purine alkaloid rich in the tender leaves of an unusual Chinese tea known as Kucha. TC possessed diverse pharmacological activity including antioxidative, anti-inflammatory, analgesic and anti-depressive effects.

Aim In this work, sustained release tablets of TC were intended to be developed with insoluble matrix material to provide a kind of preparation of prolonged action.

Methods Direct tableting process and wet granulation tableting process were screened for preparing insoluble matrix tablets of TC. Single factor testes were carried out for the formulation optimization by using drug release behaviour as evaluation index. The parameter f_2 was used to assess the similarity of the drug release behaviour of TC tablets prepared by different formulations. The common quality of TC tablets prepared by optimized formulation was investigated as well.

Results With ethyl cellulose (EC) as sustained matrix material, lactose as filler, aerosil as lubricant and anhydrous ethanol as moistening agent, the TC insoluble matrix tablets of sustained release were successfully

prepared by wet granulation tableting method. The prepared TC tablets showed no obvious burst effect with about 40% released within 2 h, and TC was almost completely released within 12 h with an accumulative drug release percentage of 84.89%. The results of common examination showed that the TC tablets were in line with the requirements of Chinese Pharmacopoeia.

Conclusion TC tablets of good sustained release behaviour were prepared simply by wet granulation tableting process with EC as release control materials. This work provided scientific evidence for development of TC preparation of prolonged action.

Key words Theacrine; sustained release; insoluble matrix tablets; process and formulation.

INTRODUCTION

Camellia assamica var. *kucha* Chang et Wang is a kind of tea plant endemic to the wild woods of Yunnan, which grows above 1000 m of altitude. Kucha has been consumed as a tea for a long time[1], and it is rich in different kinds of purine bases[2]. Theacrine (1,3,7,9-tetramethyluric acid, TC) is one of them with a structure similar to caffeine, the predominant purine alkaloid found in traditionally cultivated tea plants[3]. TC was discovered by chance from the waste after extracting caffeine from tea by Johnson in 1937[4], and its structure was determined then[5]. However, its content was very low in common tea and it was difficult to be detected. Pulse-chase experiments using Kucha leaves demonstrated that TC was synthesized by a multistep reaction involving hydration, oxidation and methylation of adenosine and caffeine. Moreover, the chemical synthesis of TC was expensive and difficult.

Kucha is natural plant resource rich in TC, which was discovered for the first time. TC was found in leaves of Kucha at all stages of growth although its concentration decreased with age. Consequently, the highest TC content was found in the expanding buds and young leaves of Kucha (~2.8% of dry weight) with diminishing amount found in mature leaves (~1.3%)[3, 6]. Pure TC could be extracted from Kucha leaves and separated through high-speed counter-current chromatography using eluent solvent system composed of hexane:dichloromethane:methanol:water (1:5:4:2, ratio by volume)[7].

TC was reported to possess diverse pharmacologic activity, including antioxidative[8], anti-inflammatory/analgesic[1] and anti-depression effects[9]. It was found that long-time drinking of Kucha brought the local people with enhanced memory and cheerful mood. Xie Guo *et al.* [9] explored the anti-depression effect and mechanism of TC in mice after oral administration by using tail suspension test, forced swimming test, spontaneous locomotor activity test, yohimbine toxicity potentiation test, reserpine reversal test and 5-hydroxytryptophan induced head-twitches test. The results showed that TC improved the activity of mice in behavioural despair and autonomic activity condition, and demonstrated good anti-depression effect in a variety of models. Its antidepressant effect may be related to increasing the content of monoamine neurotransmitter in brain, reducing the activity and expression of related receptors. Ming Guo *et al.* [10] investigated the therapeutic effect of TC on arthritis and its mechanisms in Freund's incomplete adjuvant (FIA)-induced SD rats. It was found that TC decreased the level of IL-6 and increased the level of TGF-β. Histopathological examination indicated that TC rescued the synovial hyperplasia and inflammatory cell infiltration in joint tissues. In addition, TC enhanced TGF-β-mediated shifts in inflammatory marker expression in joint tissue. It demonstrated that TC exerted a superior anti-arthritic effect via the suppression of IL-6 and the activation of TGF-β by the TGF-β/SMAD pathway.

Sustained release system can maintain an effective drug concentration in systemic circulation over an extended period of time and offer advantages such as controlled release rate, improved efficacy, or reduced dosing frequency. In oral sustained release drug delivery systems, matrix tablets have been widely used because of their simple preparing process and low-cost[11]. In matrix tablets, active ingredients were homogeneously dispersed in matrix-forming polymer materials which controlled the drug release behaviour. The matrix tablets can be prepared by simple direct compression of powder mixture of drug, polymers and other excipients, and by tableting after some sophisticated processes like granulation, spray-drying and solid dispersion

as well[12]. Insoluble matrix tablet is a kind of matrix tablets made of non-toxic plastics and high molecular polymers which were insoluble in water or have little water solubility. The commonly used insoluble matrix materials include ethyl cellulose (EC)[13], Kollidon® SR[14], polypropylene[15], Eudragit® RS (RS)[16], Eudragit® RL (RL)[17] and Eudragit® NE (NE)[18]. In order to adjust the drug release rate, electrolytes (sodium chloride, potassium chloride or sodium sulfate), sugar (lactose, fructose, sucrose or mannitol, etc.) and hydrophilic gels (hydroxypropyl methyl cellulose, carboxymethylcellulose sodium or tragacanth) were generally added as release adjusting agents in formulation.

At present, although there were TC products on the market as well as patents disclosing the pharmaceutical dosage forms of TC, they were mainly liquid preparations with TC addition as healthcare products. In this work, we intended to develop a sustained release pharmaceutical preparation of TC with insoluble matrix materials which may match the future demand of clinical application of TC based on its diverse pharmacological action. Different preparing processes and formulations were screened to achieve the insoluble matrix tablets of TC with optimized characteristics.

MATERIAL AND METHODS

MATERIALS

Theacrine was synthesized with a purity not less than 98.5%. Microcrystalline cellulose (MCC), magnesium stearate (MS) and aerosil were obtained from Shanghai Houcheng Fine Chemical Co. Ltd. (Shanghai, China). Starch and lactose were obtained from Shanghai Aladdin Co. Ltd. (Shanghai, China). Ethyl cellulose (EC), Eudragit RS (RS), Eudragit RL (RL) and Eudragit NE (NE) were obtained from Evonik Specialty Chemicals (Shanghai) Co., Ltd. (Shanghai, China). All other chemicals were commercially available and analytical grade.

PREPARING PROCESS OF INSOLUBLE MATRIX TABLETS OF TC

By using direct tableting process and wet granulation tableting process, insoluble matrix tablets of TC of 50 mg/tablet were prepared. All excipient were screened through 80 mesh sieve before use. When using direct tableting process, TC and excipients were weighed, mixed well and then compressed into tablets. When using wet granulation tableting process, the mixed powder of TC and excipients was added with moistening agent to make wet mass. The wet mass was then passed through 20 mesh sieve to obtain wet granules. After drying and sizing the granules, the dry granules were mixed well with lubricant and then compressed into tablets.

COMMON QUALITY EXAMINATION OF TC TABLETS

As described in general rule 0101 and 0923 in Appendix of Chinese Pharmacopoeia (2020 edition), weight variation test and friability test was carried out. The limit of weight variation was ±7.5% due to the tablet weight was less than 0.30 g. The weight loss limit of the friability test was not more than 1%.

DRUG RELEASE TEST OF TC TABLETS

As described in general rule 0931 in Appendix of Chinese Pharmacopoeia (2020 edition), the basket method was used to perform the drug release test of TC insoluble matrix tablets. In order to simulate the gastrointestinal environment after oral administration, dilute hydrochloric acid solution (pH = 1) was used as the release medium for the first 2 hours, then the medium was replaced with phosphate buffer solution (PBS, pH = 6.8), the temperature and rotation speed of the test was 37 ± 0.5 ℃ and 100 rpm, respectively. The release samples were taken at 15 min, 30 min, 45 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h and 12 h, respectively, with same volume of fresh release medium added at the same time. After filtered through microporous membrane of 0.45μm, the absorbance of filtrate was measured at 293 nm using early established ultraviolet (UV)-visible spectrophotometry. The accumulative drug release percentage (Q) was calculated and drug release curve was plotted.

$$Q\ (\%)\ = \frac{C_t V}{W_0} \times 100\%$$

C_t: sample concentration at time of t (μg/mL); V: volume of release medium (mL); W_0: Total amount of drug contained in the theacrine tablet for test (μg).

The difference between the release curves prepared by different formulations was compared by calculating the similarity coefficient f_2. The calculation formula is as follows.

$$f_2=50 \times \lg\left\{\left[1+\frac{1}{n}\sum_{i=1}^{n} W_i(R_i - T_i)^2\right]^{-0.5} \times 100\right\}$$

n: number of sampling points; W_i: weight factor, which is generally 1; R_i: the release percentage of the reference sample at sampling point i; T_i: the release percentage of tested sample at sampling point i.

FORMULATION SCREENING OF TC INSOLUBLE MATRIX TABLETS

Single factor test was employed to screen the formulation of insoluble matrix tablets of TC. The influence of type and amount of matrix materials, fillers, lubricants and moistening agents on quality of TC tablets was investigated. The common quality examination items of weight variation and friability was measured as well as drug release behaviour which directly exhibited the sustained release capacity caused by different formulations. The quality of TC tablets prepared by optimized formulation and process was finally examined.

STATISTICAL ANALYSIS

The data were expressed as mean ± standard deviation (SD).

RESULTS AND DISCUSSION

PREPARING PROCESS OF TC INSOLUBLE MATRIX TABLETS

Direct tableting process of powder had advantages of time saving and energy saving due to few steps in preparation, but it has high requirements on the flowability and compressibility of the powder materials. Wet granulation tableting process is a widely used conventional method suitable for drugs not sensitive to heat and moisture, which generally gives the powder materials good flowability, compressibility and compactibility to obtain tablets of good appearance and strong resistance to abrasion. In this work, only TC tablets prepared with EC as matrix material showed enough hardness when using direct tableting process. However, the drug release was not complete enough with an accumulative release percentage less than 70% at 12 h. When using wet granulation tableting process, it was easy to prepare TC insoluble matrix tablets fitting quality requirements using different matrix materials and excipients. Therefore, wet granulation tableting process was selected for subsequent formulation screening.

FORMULATION SCREENING OF TC INSOLUBLE MATRIX TABLETS

In this part, common quality examination and drug release behaviour (especially accumulative release percentage at 2 h and 12 h, Q_2 and Q_{12}) was used for evaluating the quality and sustained release characteristics of TC insoluble matrix tablets. The sustained release behaviour was the key point for investigation, so the similarity factor (f_2) was calculated for comparison. The f_2 value was used to establish similarity of two release curves[19]. It is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent of release between the two curves. The larger the difference between two drug release curve, the smaller the f_2 value. When $f_2 < 50$, the difference between the two release curves was considered significant. When $50 < f_2 < 100$, the two release curves was thought to be similar and the similarity increases with the increase of f_2 value.

Base on the pilot experiment, the following formulation was used as basic formulation for screening by single factor tests. Ethyl cellulose (EC), lactose, ethanol and magnesium stearate (MS) were used as matrix material, filler, moistening agent and lubricant, respectively, and the ratio of EC to lactose was 1:1. The tablets were prepared by wet granulation tableting process.

MATRIX MATERIALS TYPE

On the basis of basic formulation, different matrix materials, including EC, Eudragit RS (RS), Eudragit RL (RL) and Eudragit NE (NE), were used to prepare TC tablets with the other conditions fixed unchanged, respectively. The influence of matrix materials on quality of TC tablets was showed in **Table 1** and **Figure 1**. The weigh variation and friability of the tablets prepared by four matrix materials were all met the requirements. In terms of drug release, the tablets prepared with EC, RS and NE had obvious sustained release effect, while more than 98% TC in tablets with RL was released at 2 h. Although RS and NE showed stronger sustained release capacity, the accumulative drug release percentage was less than 70% at 12 h, which might result in incomplete drug release. Tablets with EC showed a burst effect to some extend but released TC more completely than tablets with RS and NE. The release curve of tablets with EC shown better stable sustained release. Compared with the tablets prepared with EC, the f_2 values of TC tablets prepared with RL, RS and NE were 28.56, 35.11 and 30.39, respectively, which were all less than 50. It indicated that there was significant difference between the release curve of tablets prepared with EC and that of tablets prepared with the other three materials. Therefore, EC was selected as optimized matrix material to prepare tablets in the following experiments.

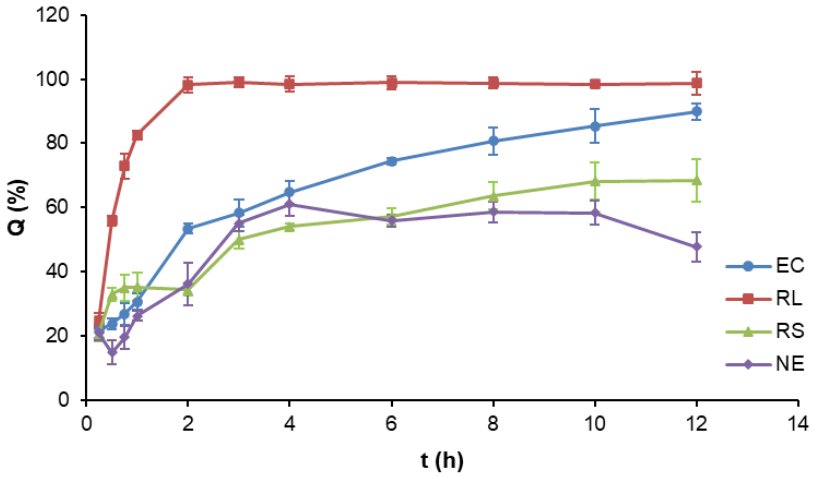

Figure 1 The drug release curves of TC tablets prepared with different matrix materials. (n = 3)

Table 1 Quality control of theacrine tablets prepared with different matrix materials. (n = 3)

Matrix materials	Tablet weight variation (%)		Friability	Q_2 (%)	Q_{12} (%)
	Qualified or not	>±7.5% (Tablet)			
EC	Qualified	0	Qualified	53.47±1.65	89.92±2.50
RL	Qualified	0	Qualified	98.26±2.36	98.96±3.52
RS	Qualified	2	Qualified	34.33±1.76	68.50±6.71
NE	Qualified	0	Qualified	36.20±6.53	47.67±4.71

* Q_2 (%) and Q_{12} (%) were the accumulative release percentage of the tablets at 2 h and 12 h, respectively.

FILLERS TYPE

On the basis of basic formulation and the above screening results, different fillers, including lactose, starch and microcrystalline cellulose (MCC), were used to prepare TC tablets with the other conditions fixed unchanged, respectively. Except starch, TC tablets were smoothly prepared with MCC and lactose. The influence of MCC and lactose on tablets quality was listed in **Table 2** and the drug release curve was illustrated in **Figure 2**. The f_2 value of the two drug release curves was 67.78 indicating good similarity of the drug release behaviour of the two kinds of tablets. The value of Q_2 and Q_{12} was significantly different between the two kinds of tablets. The tablets prepared with MCC showed more than 87% release of TC and no more drug released then. The tablets with lactose exhibited lower burst effect at 2 h and more complete drug release at 12 h. According to the results, lactose was chosen as filler for further experiments.

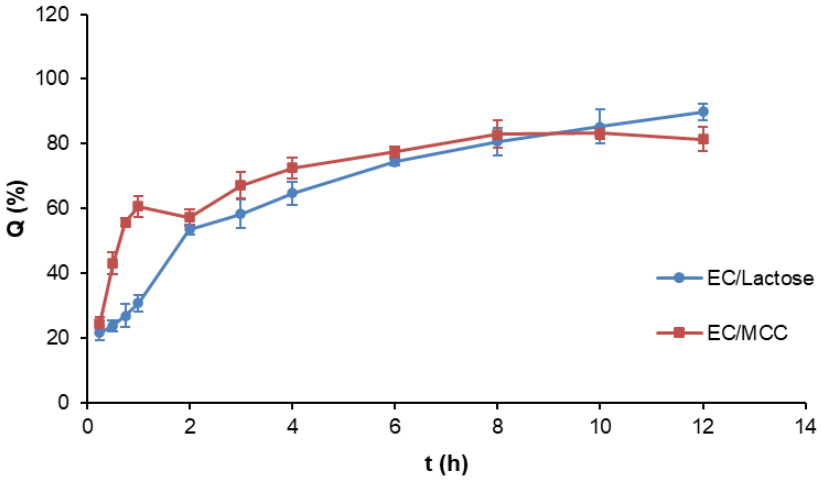

Figure 2 The drug release curves of TC tablets prepared with different fillers. (n = 3)

Table 2 Quality control of theacrine tablets prepared with different fillers. (n = 3)

Matrix materials /fillers	Tablet weight variation (%)		Friability	Q_2 (%)	Q_{12} (%)
	Qualified or not	>±7.5% (Tablet)			
EC/Lactose	Qualified	0	Qualified	53.47±1.65	89.92±2.50
EC/MCC	Qualified	0	Qualified	57.30±2.61	81.42±3.65

* Q_2 (%) and Q_{12} (%) were the accumulative release percentage of the tablets at 2 h and 12 h, respectively.

TYPE AND AMOUNT OF LUBRICANTS

On the basis of basic formulation and the above screening results, MS and aerosil were used as lubricant to prepare TC tablets with the other conditions fixed unchanged, respectively. The results were shown in **Table 3** and **Figure 3**. As shown in **Figure 3**, TC tablets prepared with aerosil achieved more complete drug release, so aerosil was selected as lubricant for further amount screening.

The tablets were then prepared with different amount of aerosil, and the common quality and drug release behaviour of TC tablets was measured and the results were shown in **Table 4** and **Figure 4**. With the increase of aerosil amount, the release at 2 h decreased and the release at 12 showed no obvious change. The f_2 values between release curve of tablets with 1% aerosil and that of tablets with 2%, 3% were 88.31 and 69.76, respectively. It indicated that the drug

release behaviour was similar between tablets. Also, the amount of aerosil had no effect on the preparing procedure and common quality of the tablets, so the amount of aerosil was determined as 1% for further study.

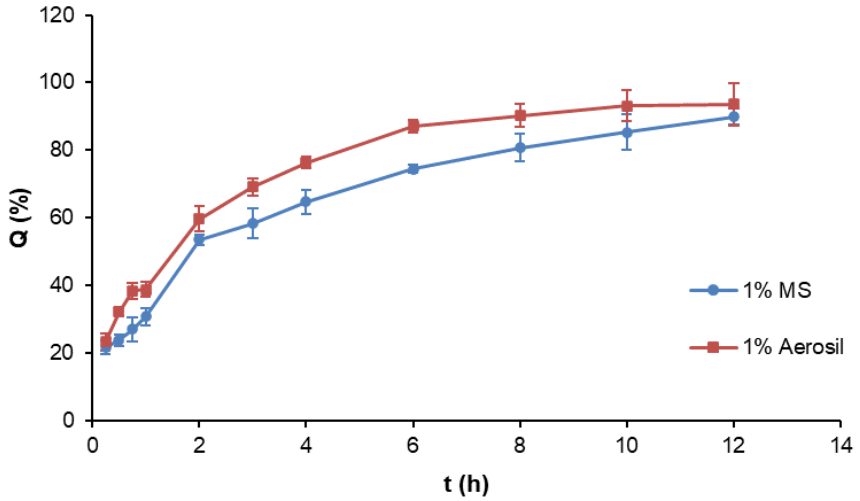

Figure 3 The drug release curves of TC tablets prepared with different lubricants. (n = 3)

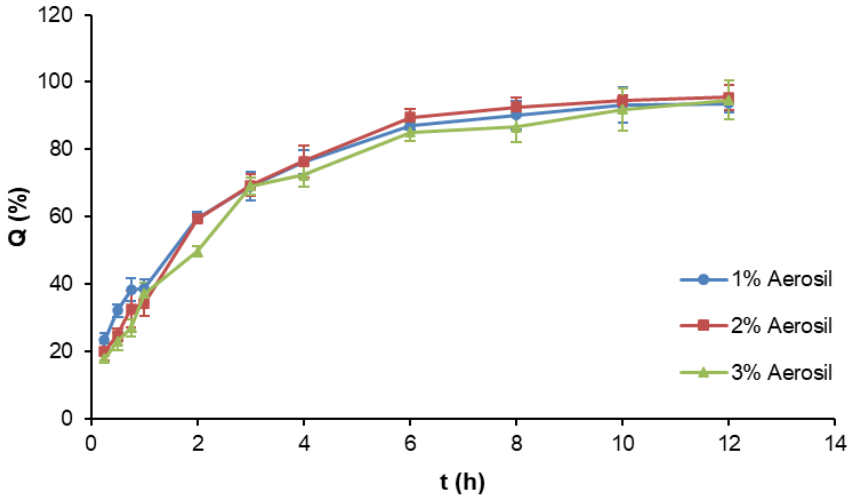

Figure 4 The drug release curves of TC tablets prepared with different amount of aerosil. (n = 3)

Table 3 Quality control of theacrine tablets prepared with different lubricants. (n = 3)

Lubricants	Tablet weight variation (%)		Friability	Q_2 (%)	Q_{12} (%)
	Qualified or not	>±7.5% (Tablet)			
1% MS	Qualified	0	Qualified	53.47±1.65	89.92±2.50
1% Aerosil	Qualified	0	Qualified	59.71±3.69	93.64±6.30

* Q_2 (%) and Q_{12} (%) were the accumulative release percentage of the tablets at 2 h and 12 h, respectively.

Table 4 Quality control of theacrine tablets prepared with different amount of aerosil. (n=3)

Aerosil	Tablet weight variation (%)		Friability	Q_2 (%)	Q_{12} (%)
	Qualified or not	>±7.5% (Tablet)			
1%	Qualified	0	Qualified	59.71±3.69	93.64±6.30
2%	Qualified	0	Qualified	59.40±1.47	95.46±3.84
3%	Qualified	0	Qualified	49.69±1.49	94.59±5.75

* Q_2 (%) and Q_{12} (%) were the accumulative release percentage of the tablets at 2 h and 12 h, respectively.

MOISTENING AGENT CONCENTRATION

On the basis of basic formulation and the above screening results, anhydrous ethanol, 80% ethanol and 60% ethanol were used as moistening agent to prepare TC tablets with the other conditions fixed unchanged, respectively. The results were shown in **Table 5** and **Figure 5**. Compared with the release curve of tablets prepared with anhydrous ethanol, f_2 value of tablets prepared with 80% and 60% ethanol was 36.99 and 46.34, respectively, indicated low similarity between the release curves. As shown in **Table 5** and **Figure 5**, the weight variation and friability of the tablets prepared with different concentration of ethanol solution met the requirements and the tablets with anhydrous ethanol showed the most complete release of TC at 12 h. Therefore, anhydrous ethanol was selected as moistening agent for subsequent experiments.

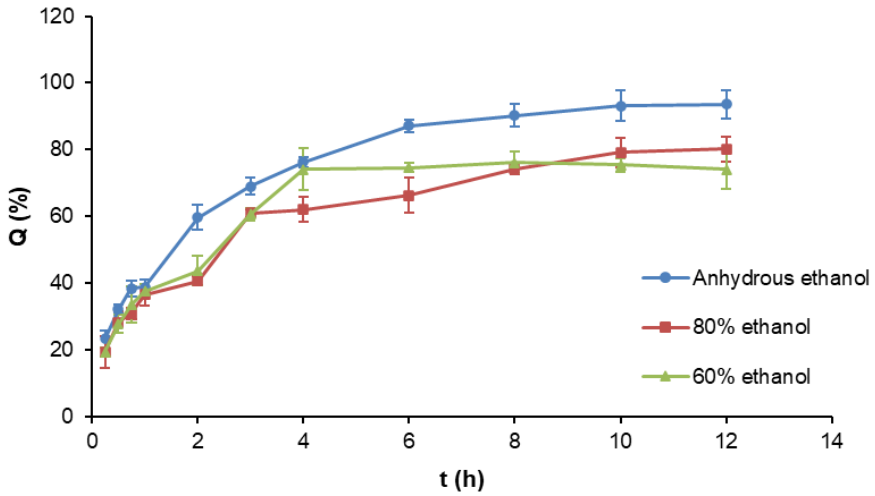

Figure 5 The drug release curves of TC tablets prepared with ethanol of different concentration. (n = 3)

MASS RATIO OF MATRIX MATERIAL TO FILLER

Through the above screening, insoluble matrix tablets of TC of good appearance and common quality were prepared and the tablets released drug slowly and completely. However, the release of TC was somewhat fast at 2 h. In this part, the mass ratio of matrix material to filler was further screened because the amount of matrix material directly affects the sustained release characteristic. TC tablets were prepared with EC and lactose at different mass ratio of 2:3, 5:6, 1:1, 6:5 and 3:2 (EC:lactose). The results demonstrated that both the value of Q_2 and Q_{12} was increased and then decreased with the increase of EC amount. The TC tablets prepared with EC and lactose at a ratio of 6:5 exerted the lowest burst release percent at 2 h, and the release at 12 h was also complete with about 85% TC released (**Table 6**). The drug release curve showed that drug released slowly and stably from TC tablets prepared with EC and lactose (6:5), which

achieved perfect sustained release behaviour (**Figure 6**). Compared with the tablets prepared at the ratio of 6:5, the f_2 values of drug release curves of tablets prepared at the other four ratios were 35.48 (2:3), 46.88 (5:6), 38.09 (1:1) and 41.54 (3:2), respectively. The drug release behaviour was not similar between TC tablets prepared with EC and lactose at different mass ratios. Based on the results, the ratio of EC to lactose of 6:5 was selected as the optimized one which achieved the expected sustained release behaviour.

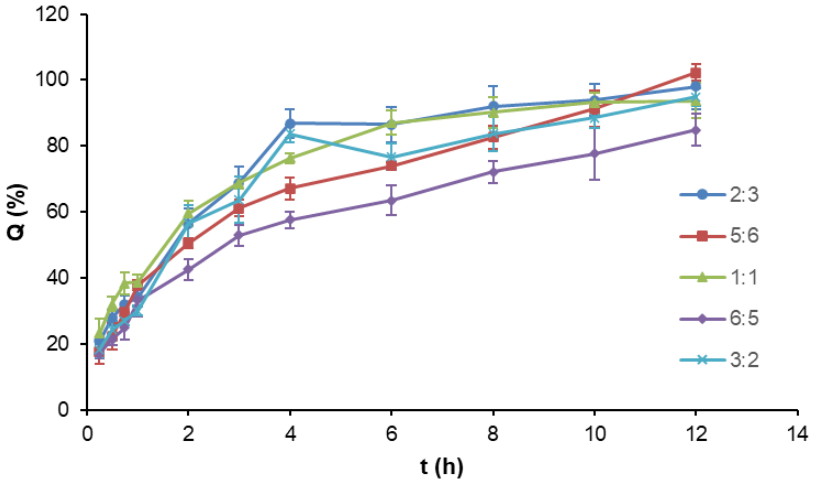

Figure 6 The drug release curves of TC tablets prepared with different ratio of matrix material to fillers. (n=3)

Through the above single factor tests, the optimized formulation was determined to produce TC insoluble matrix tablets of perfect sustained release behaviour. The TC tablets were prepared with EC as matrix material, lactose as filler, anhydrous ethanol as moistening agent and aerosil as lubricant, and the mass ratio of EC to lactose was 6:5. The weight variation of all the randomly selected 20 tablets was less than ±7.5% and the weight loss after friability test was not more than 0.11%. The TC insoluble matrix tablets exhibited stable sustained release of drug with no obvious burst effect and relatively complete drug release.

CONCLUSION

In summary, TC insoluble matrix tablets with satisfactory quality and sustained release behaviour were prepared by wet granulation tableting process. The results shown that the types and amount of insoluble matrix materials and fillers greatly affected the compressibility, compactibility and drug release characteristics of the TC insoluble matrix tablets. The TC tablets prepared with optimized formulation were of expected stable slow release of drug with no obvious burst effect and relatively complete release. This work provided scientific evidence for developing TC preparations of prolonged action.

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Abbreviations: TC: Theacrine); 5-HTTP: 5-hydroxytryptophan; EC: Ethyl cellulose; MS: Magnesium stearate; MCC: Microcrystalline cellulose; RS: Eudragit RS; RL: Eudragit RL; NE: Eudragit NE.