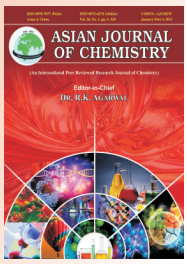
Asian Journal of Chemistry; Vol. 26, No. 15 (2014), 4723-4727

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16187



Study on Sustained-Release Tablets of Tramadol Hydrochloride

QING HUO, CHENYANG GUO*, TIANHAO GU and WANYING LIU

Biochemical Engineering College of Beijing Union University, Beijing 100023, P.R. China

*Corresponding author: Tel: +86 10 52072259; E-mail: chenyangguo09@126.com

Received: 13 August 2013; *Accepted*: 11 December 2013; *Published online*: 16 July 2014; AJC-15559

Tramadol hydrochloride has a potential role in the central nervous system of potent non-narcotic analgesics, no respiratory depression and cardiovascular reactions, is a non-morphine-like analgesics. In order to improve the analgesic effect time of tramadol hydrochloride, we study on 2 times a day for 12 h sustained-release tablets, single factor is determined by the release of different viscosity hydroxypropyl methyl cellulose (HPMC), identified by model K15M HPMC as hydrophilic matrix, orthogonal design study factors affecting sustained-release tablets, the prescription of 1000 tramadol hydrochloride sustained-release tablets is tramadol hydrochloride 69 g, carboxymethyl cellulose of sodium 20 g, hydroxypropyl methyl cellulose 27 g, PEG 15.41 g, ethyl cellulose 13.40 g, magnesium stearate 6 g, starch 2 g, the limitation of l, 2, 4, 8 h of dissolution for tramadol hydrochloride are 32, 42, 68 and 85 %, the average tablet weight 0.15 g, hardness 5.28 kg in the pharmacopoeia range. The stability of tablets is measured in the illumination of 2000-4000 LX, quality does not change and no degradation products, when the tablets are put in a high temperature of 80 °C, the surface of the tablets become yellow, so tablets should be sealed and placed in cool place.

Keywords: Tramadol hydrochloride, Hydrophilic matrix, Hydroxypropyl methyl cellulose, Sodium carboxymethyl cellulose.

INTRODUCTION

Tramadol hydrochloride *i.e.*, (1R,2R)-rel-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol is a centrally acting synthetic non-narcotic analgesic, as well as a weak opioid receptor agonist used to treat moderate to moderately severe pain. The drug has a wide range of applications, including treatment of rheumatoid arthritis, restless legs syndrome, motor neurone disease and fibromyalgia. Tramadol has been demonstrated to provide superior analgesia and duration, unlike other opioids, tramadol has no clinically relevant effects on respiratory depression or cardiovascular parameters as long as under the recommend dose and it's drug abuse and dependence[1,2], side effects are of minor clinical relevance. It was launched and marketed by the German pharmaceutical company Grünenthal GmbH in 1977. Now tramadol has been widely used and sold globally. Ever since, cause the significant characteristic of tramadol, it got more and more concerned in the realm of pharmacy[3-5].

Sustained-release formulations were debuted and defined in 1980s, over a few years, this development come about rather quickly. Sustained-release technology is a mechanism which used in pill tablets or capsules to dissolve a drug over time in order to be released slower and steadier into the bloodstream while having the superiority of being taken at less frequent intervals than immediate-release (IR) formulations of the same drug and improve the patient compliance[6]. Cause its lasting curative function, lower side-effect and less applied time, now it's proved to be the major part of the drug delivery system.

Today, the most common way is to embedding the active ingredient tablet in a matrix of insoluble substance while its main material is the hydroxypropyl methyl cellulose (HPMC). The HPMC viscosity is the main factor influencing the active ingredient release from HPMC extended matrix tablet. There are three major specification of HPMC (K4M, K15M, K100M)[7].

This paper study the influence of the different HPMC viscosity to study the quality and the stability of the matrix tablet, meanwhile search a superior prescription process. The employment of the matrix HPMC, prepares a tramadol hydrochloride sustained release tablets which could completely released in 12 h and the tablet's *in vitro* level could approved by the FDA.

EXPERIMENTAL

Tramadol hydrochloride (Pu Ren Pharmaceutical Co. Ltd. in Suzhou); hydroxypropyl methyl cellulose(HPMC), PEG6000 (polyethylene glycol), amylum (Beijing Chemical Reagent Company); sodium carboxymethyl cellulose (Tianjin Fuchen Chemical Reagent Factory); ethyl cellulose (Hanson Shanghai Chemical Reagent Company); ethanol (Beijing Chemical Plant); distilled water: prepared in laboratory.

UVmini-1240 spectrophotometer (Puxi Radio Factory); T-214 electronic balance (Beijing sartorius Instrument System Co. Ltd); DH-202 type Constant Temp Oven (Tianjin Zhonghuan test Electric Co. Ltd); Q/HDHHL002-2003 type single-punch tablet press (Shanghai Tianfan pharmaceutical machinery factory); ZRS-8G Dissolution Tester (Tianjin University Radio Factory); KH-250D Bultrasonic cleaner (Kunshan Hechuang Instrument Co.Ltd); YD-3 Hardness Tester (Tianjin Guoming medicine equipment Co. Ltd.); CJY-300D tablet friability & hardness tester (Shanghai the Yellow Sea Medical Instrument Co. Ltd.); LS-3000 Drugs in low temperature light tester (Shanghai Jinpeng analytical instruments Co.Ltd.).

Preparation method: (1) The material is, respectively crushed, sieved (sieve mesh number 80); (2) The material is respectively weighed as requested and mixed in proportion; (3) Add adhesive, prepared by using high speed stirring machine; (4) Dried in 50-60 °C; (5) Sieve(sieve mesh number 12-16); (6) Lubricant is added in proportion, mix, with a diameter of the die F5 mm direct compression (Fig. 1).

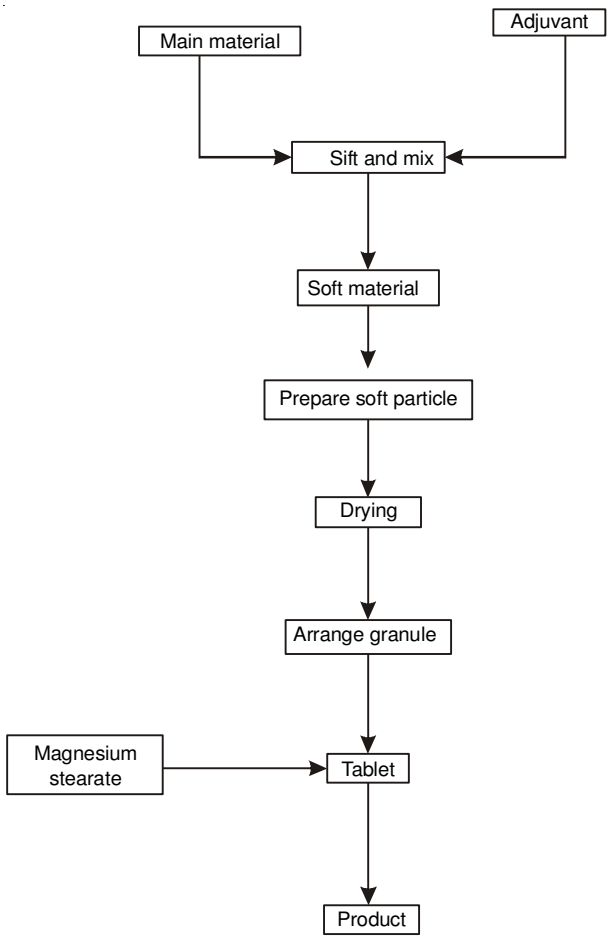


Fig. 1. Technological process of the wet granulation

Analytical method: UV analysis is applied to determine the content of tramadol hydrochloride. Dissolve 50 mg tramadol hydrochloride in 100 mL water, then separately weigh 0.5, 1.0, 1.5, 2, 2.5 mL solution and dilute with water to 25 mL, tramadol hydrochloride concentration is calculated using the standard sample as the calibration standard. A good linear relationship is obtained over the range of 10 μg/mL < C < 50 μg/mL and the regression is y = 0.02x + 0.14 (R = 0.9998), where y is the absorbance at 267 nm, x is the concentration of Chlorogenic acid (mg mL^{-1}) and R is the regression coefficient.

Method of measuring release rate: Take samples, according to the release determination method, using the method of dissolution test method first device, 900 mL water is released medium, speed is 100 rpm/min, according to the first method of operation, at the time of 1, 2, 4, 8, 12 h, take 10 mL solution, filtration and immediately add the same volume, the same temperature of the water, the concentration of filtrate (C) is measured by UV-visible spectrophotometry, main ingredients per tablet is 0.04 g.

$$\text{Release rate} = 900 \times C \times 10^{-6}/0.04$$

RESULTS AND DISCUSSION

Effect on the releasing rate with different viscosity: The impact of HPMC viscosity on *in vitro* release rate of tramadol hydrochloride, HPMC as hydrophilic matrix tablet is evident (commonly using) HPMC K4M (viscosity number 4000 cps), HPMC K15M (viscosity number 15000 cps) and HPMC K100M (viscosity number 100000 cps). We design prescriptions which select the best type of HPMC, as well as to determine the release rate. Different HPMC sustained release tablet prescription see Table-1, release rate and releasing curve see Table-2 and Fig. 2.

With HPMC as hydrophilic matrix, the effect of *in vitro* release is directly related to the viscosity of HPMC.

TABLE-1
DIFFERENT HPMC SUSTAINED RELEASE TABLET PRESCRIPTION

Material and accessory	Prescription 1	Prescription 2	Prescription 3
Tramadol hydrochloride	1.00 g	1.00 g	1.00 g
HPMC K4M	0.60 g	–	–
HPMC K15M	–	0.60 g	–
HPMC K100M	–	–	0.60 g
Mgnesium stearate	Suitable amount	Suitable amount	Suitable amount

TABLE-2
RELEASE RATE OF DIFFERENT VISCOSITY HPMC

Prescription	Release rate (%)			
	1 h	2 h	4 h	8 h
Prescription 1	39.21	48.43	65.15	88.32
Prescription 2	40.42	51.29	66.38	88.43
Prescription 3	41.83	55.39	70.76	90.30

Fig. 2 showed that there is no evident difference in those three dissolution curves of drug release of tablets which by using different type of HPMC in tablets (K4M, K15M, K100M). Due to the less cost of HPMC K15M, it is finally chosen as the matrix in the tablet.

Experiment of influencing factor in the drug release of tablets: The orthogonal table is designed according to four factors and three levels (Tables 3 and 4). Four variables are sodium carboxymethyl cellulose (CMC), hydroxypropyl methyl cellulose (HPMC) (K15), PEG (6000) and ethyl cellulose (EC).

TABLE-4
RESULTS AND CALCULATIONS OF $L_9(3)^4$

Test	Level of factor				Release rate (%)			
	CMC (g)	HPMC(K15) (g)	PEG6000 (g)	EC (g)	1 h	2 h	4 h	8 h
1	0.30	0.40	0.23	0.17	35.30	43.33	79.01	89.90
2	0.30	0.60	0.25	0.20	33.21	45.40	68.01	93.05
3	0.30	0.80	0.27	0.23	34.50	44.35	66.56	87.20
4	0.50	0.40	0.25	0.23	27.52	37.34	47.37	76.69
5	0.50	0.60	0.27	0.17	23.21	33.23	47.34	83.31
6	0.50	0.80	0.23	0.20	22.12	36.60	52.81	89.01
7	0.70	0.40	0.27	0.20	26.17	37.27	51.93	83.73
8	0.70	0.60	0.23	0.23	21.05	37.20	64.31	84.51
9	0.70	0.80	0.25	0.17	25.31	39.80	49.98	72.62

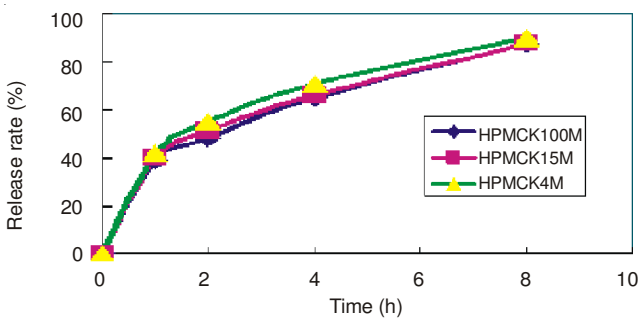


Fig. 2. Influence of different HPMC viscosities on the release rate of tablet

TABLE-3
3 LEVELS AND 4 FACTORS GRAPH

Level	CMC (g)	HPMC (K15) (g)	PEG (6000) (g)	EC(g)
1	0.3	0.4	0.23	0.17
2	0.5	0.6	0.25	0.20
3	0.7	0.8	0.27	0.23

Process the data of the release rates in 1 h, 2 h, 4 h, 8 h, respectively, calculating the sum, average and the extremum R (Tables 5-8).

TABLE-5
PROCESS DATA OF RELEASE RATE IN 1 h

Level of factor	CMC	HPMC(K15)	PEG6000	EC
K1	34.34 %	29.66 %	26.16 %	27.94 %
K2	27.26 %	25.82 %	32.01 %	27.20 %
K3	24.18 %	27.31 %	27.96 %	31.02 %
R	10.16	3.84	5.85	3.82

TABLE-6
PROCESS DATA OF RELEASE RATE IN 2 h

Level of factor	CMC	HPMC(K15)	PEG6000	EC
K1	44.36 %	39.31 %	39.04 %	38.79 %
K2	35.72 %	38.61 %	40.85 %	39.76 %
K3	38.09 %	40.25 %	38.28 %	39.63 %
R	8.64	1.64	2.57	0.97

TABLE-7
PROCESS DATA OF RELEASE RATE IN 4 h

Level of factor	CMC	HPMC(K15)	PEG6000	EC
K1	79.19 %	59.44 %	65.38 %	58.78 %
K2	49.17 %	59.89 %	55.12 %	57.58 %
K3	55.41 %	56.45 %	55.28 %	59.41 %
R	22.02	3.44	10.26	1.83

TABLE-8
PROCESS DATA OF RELEASE RATE IN 8 h

Level of factor	CMC	HPMC (K15)	PEG6000	EC
K1	90.05 %	83.44 %	87.81 %	81.94 %
K2	83.00 %	86.96 %	80.79 %	88.60 %
K3	80.29 %	82.94 %	84.75 %	82.8 %
R	9.76	4.02	7.02	6.66

The range analysis shows the contents of all adjuvant which effect the release rate of tramadol hydrochloride. In comparison with the influence of four different adjuvants (CMC, HPMC, PEG, EC) to the release, the amount of CMC has remarkable effect on the release rate, the effect of the content of EC on the release rate is the least significant. The best combination of adjuvant are CMC13.33 %, HPMC17.78 %, PEG(6000)10.22 %, EC 8.89 %. The prescription of 1000 tablets of tramadol hydrochloride sustained-release are determined which are tramadol hydrochloride: 67 g; CMC: 20 g; HPMC (K15): 27 g; PEG(6000): 15.41 g; EC: 13.40 g; magnesium stearate: 2 g; amylum: 6 g.

Analysis and inspection of prescription

Repeatability tests: According to the above prescription, prepare three small batches of tramadol hydrochloride sustained-release tablets, release rates are measured separately, the test data are shown in Table-9 and Fig. 3.

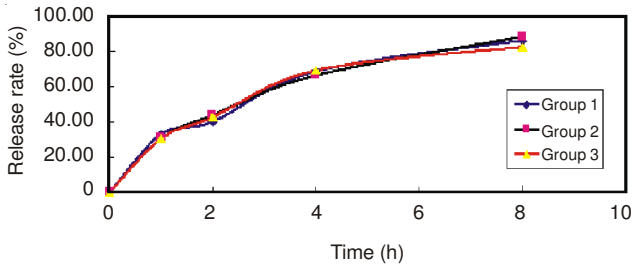


Fig. 3. Release curve of three batches of tramadol hydrochloride sustained-release tablets

TABLE-9
RELEASE RATE OF THREE BATCHES OF TRAMADOL HYDROCHLORIDE SUSTAINED-RELEASE TABLETS

Groups	Release rate (%)			
	1 h	2 h	4 h	8 h
1	33.15	40.22	68.83	86.25
2	30.79	44.01	66.51	88.42
3	30.66	42.79	69.39	82.61

According to Fig. 3, release curves of three batches of tablets have the same trend, release rate can be up to standard, the quality of tablets is stable and repeatable.

Tablet weight and hardness test: Twenty tramadol hydrochloride tablets are accurately weighed, calculate the average weight of tablets. Comparing with the weight of per tablet which measured before, the range of tablet weight is shown in Table-10.

TABLE-10
WEIGHT OF THE TABLET TEST DATA

Weight of 20 tablets (g)	Average (g)	Range (g)
0.1527, 0.1538, 0.1500, 0.1544, 0.1493, 0.1559, 0.1533, 0.1452, 0.1489, 0.1501, 0.1623, 0.1521, 0.1574, 0.1462, 0.1498, 0.1501, 0.1438, 0.1541, 0.1456, 0.1447	0.1500	0.1388-0.1613

Pharmacopoeia: When the average weight of tablets is below 0.30 g, the weight difference limit is ± 7.5 %, so this experiment tablet weight variation range should be in 0.1388-0.1613 g. In the test, the range of weight variation is 0.1438-0.1623 g, only one tablet weight 0.1623 g not within the range, the other 19 tablets are within the specified range, because the overweight tablet does not exceed twice as much as the weight limit, so the weight difference comply Pharmacopoeia.

Respectively fixing 20 tablets of tramadol hydrochloride sustained-release tablets in the spring of hardness tester and pressurized it to pulverizing, the hardness of the tablet test data is shown in Table-11. The test showed that hardness values of 20 tablets are in line with the provisions.

TABLE-11
HARDNESS OF THE TABLET TEST DATA

Hardness of 20 tablets (kg)	Average of hardness (kg)
5.43, 5.37, 4.98, 5.22, 5.14, 5.47, 5.31, 5.29, 5.42, 5.28, 5.11, 5.32, 5.44, 5.32, 5.17, 5.39, 5.07, 5.41, 5.19, 5.35	5.28

Friability test: Blowing powder firstly, 44 pieces of tramadol hydrochloride sustained-release tablets weigh 6.5981 g, put them in friability tester, turn 100 times, remove the powder on the surface of tablets with a hair dryer, then weigh 6.5437 g, weight loss does not exceed 1 %, no breaks, cracks and powder of a tablet are detected.

Stability test

Illumination experiment: Place the tablets on the dish under the condition of the illumination between 2000- 4000LX for 10 days, the samples are taken on the 1st, 3rd, 5th, 10th day, test release rate of sample within 8 h, the results are shown in Table-12.

The results show that in 2000-4000Lx light intensity condition, the basic quality of the sample does not change, no degradation products, the indicators are in line with requirements.

Heat-resisting test: Place the tablets on the dish under 40, 60 and 80 °C condition for 10 days, the samples are taken on the 1st, 3rd, 5th, 10th day, test release rate of sample within 8 h, the results are shown in Tables 13 and 14.

The results show that at 40 °C, quality of the sample did not change much, no degradation products, the indicators are in line with regulations; while at 60 °C, release rate become

TABLE-12
RESULTS OF ILLUMINATION TEST

Time (d)	Exterior	Release rate (%)			
		1h	2h	4h	8h
0	White	32.43	41.68	69.05	88.37
1	White	33.29	40.55	69.99	89.97
3	White	33.91	42.37	70.53	89.09
5	White	32.01	41.15	68.99	87.62
10	White	32.44	42.34	70.71	91.07

TABLE-13
RESULTS OF THERMOSTABILITY TEST UNDER 40°C

Time (d)	Exterior	Release rate (%)			
		1h	2h	4h	8h
0	White	32.43	41.68	69.05	88.37
1	White	31.65	43.31	78.01	91.33
3	White	35.13	45.21	70.43	83.29
5	White	30.31	40.11	64.03	88.33
10	White	37.49	41.76	73.53	90.23

TABLE-14
RESULTS OF THERMOSTABILITY TEST UNDER 60 °C

Time (d)	Exterior	Release rate (%)			
		1 h	2 h	4 h	8 h
0	White	32.43	41.68	69.05	88.37
1	White	37.52	49.01	79.03	93.46
3	White	39.21	50.33	83.42	89.88
5	White	36.74	47.41	80.47	89.90
10	White	38.63	49.53	77.05	90.11

TABLE-15
RESULTS OF THE RELEASE RATE IN AIR AT ROOM TEMPERATURE

Time (d)	Exterior	Release rate (%)			
		1 h	2 h	4 h	8 h
0	White	32.43	41.68	69.05	88.37
1	White	33.49	42.25	69.37	89.01
3	White	33.32	42.90	73.43	87.66
5	White	30.81	44.53	77.51	95.05
10	White	33.68	47.74	79.11	93.94

slightly faster and no degradation products, the indicators are still compliance, at 80 °C the surface of the tablet was yellow. Therefore, this product is not stored in a high-temperature environment.

Air tests: Place the tablets on the dish in air at room temperature for 10 days, the samples are taken on the 1st, 3rd, 5th, 10th day, test release rate of sample within 8 h, the results are shown in Table-15.

The results show that there are small changes in release rate in air at room temperature condition, but still meet the requirements and no degradation products, so the product should be sealed.

Conclusion

The release rate is a important parameter in the preparation of the prescription process and the quality control. By the use of HPMC as matrix, the viscosity and the amount of HPMC have remarkable effects on the release rate of tablets, we can prepare within 12 h of the full release of tramadol hydrochloride sustained-release tablets. By prescribing process control, regulate drug release behavior of pharmaceutical preparations to meet the design requirements, the drug delivery system has some theoretical and practical value, it is worth further study. This study has shown that tramadol hydrochloride tablets process route which is made by the technological process of the wet granulation is good. Low cost, stable quality, reproducible, simple operation.

REFERENCES

1. X.P. Zhang and S.J. Li, *Modern J. Integr. Tradit. Chin. Western Med.*, **14**, 1920 (2005).
2. A. Anderson, T. Stadler and J. Olligs, *Chinese J. Pain Med.*, **4**, 251 (1998).
3. S. Nossol, M. Schwarzbold and T H. Stadles, *Chinese J. Pain Med.*, **6**, 59 (2000).
4. R.A. Moore and H.J. McQuay and F. Luo, *Chinese J. Pain Med.*, **5**, 121 (1999).
5. Y. Yang and B.W. Song, *Chinese Med. Bull.*, **10**, 396 (1994).
6. State Pharmacopeia Committee of China, Chinese Pharmacopoeia (2010 version Appendix), Chinese Medical Science and Technology Press, Appendix 201 (2010).
7. C. Gustafsson, M.C. Bonferoni, C. Caramella, H. Lennholm and C. Nyström, *Eur. J. Pharm. Sci.*, **9**, 171 (1999).