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Original Research Article

Formulation and Evaluation of Tramadol HCl Matrix Tablets Using Carbopol 974P and 934 as Rate-Controlling Agents

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Abstract

Purpose: *To formulate and prepare controlled release (CR) matrix tablets of tramadol HCl using Carbopol 974P and 934 polymers as rate-controlling agents.*
Methods: *The tablets were prepared by direct compression method using various drug to polymer (D:P) ratios. Co-excipients, including carboxymethylcellulose, starch and/or hydroxypropyl methylcellulose were also used to modulate the formulations. Various physical tests and in vitro dissolution studies were carried out on the formulations. The dissolution data were subjected to various release models*
Results: *As the concentration of the polymer (rate-controlling agent) increased, dissolution rate decreased, For the formulation containing Carbopol 974P at D:P ratio of 10:7, drug release decreased to 83 % compared with the release rate of 99 % for the formulation with D:P ratio of 10:3. Kinetic analysis indicates that drug release mechanism was anomalous non-Fickian diffusion.*
Conclusion: *Both Carbopol 974P and 934 can be used as rate-controlling agents in the formulation of tramadol HCl CR tablets. Appropriate selection of drug/polymer ratio can be applied effectively to modulate the dissolution rate of the drug.*

Keywords: *Tramadol, Carbopol, Carboxymethylcellulose (CMC), Hydroxypropyl methylcellulose, Controlled release*

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INTRODUCTION

Immediate release dosage forms have negligible control on drug release from dosage form that generally leads to constantly changing, unpredictable sub or supra therapeutic drug concentrations in plasma [1]. Controlled release (CR) formulations are used to overcome the drawbacks of immediate release formulations.
Matrix system is the most widely used method for the development of CR dosage form due to its ease of manufacture. Different natural and synthetic polymers are used for CR matrix systems which have the property to extend the release of drug from matrix system [2]. In matrix systems, the release of drugs from the hydrophilic polymers is controlled by a combination of mechanisms such as polymer swelling, erosion and diffusion [3]. Carbopols or carbomers (hydrophilic polymer) compress very well and have strong binding characteristics which make them ideal for direct compression process. They show compatibility with various active ingredients and other excipients [4,5]. Carbopol 974P and Carbapol 934 are oral pharmaceutical grades of carbomers. Their

hydrophilic nature and highly crosslinked structure make them suitable candidates for CR formulations [6].

Tramadol hydrochloride, an opoid analgesic used in severe acute and chronic pain has a good bioavailability and is prescribed 3-4 times a day. This frequent dosing schedule cause increased incident of side effects, non compliances and development of tolerance especially in long term used like osteoarthritis, arthritis, post surgical pains etc [7]. It can be suggested that there is a strong clinical implication of CR formulation of this drug.

The present study has the objective of designing a CR matrix system of tramadol HCl, using Carbopol 974P and Carbopol 934 as the polymer carrier in various drug/polymer ratios.

EXPERIMENTAL

Materials

Tramadol HCl (Global Pharma, Islamabad, Pakistan), Carbopol 974P NF and Carbopol 934 (Dow Chemical Co, Midland, USA), sodium hydroxide (Merck, Germany), monobasic potassium phosphate (Merck, Germany), lactose and magnesium stearate (BDH Chemicals, Poole, England), carboxymethylcellulose CMC and starch (Velor Pharmaceuticals, Islamabad Pakistan) were used. PharmaTest dissolution apparatus (D-6312, Hainburg, Austria), single-punch tablet machine (Erweka AR-400, Germany), UV visible spectrophotometer (UVIDEC-1601, Shimadzu, Japan), hardness tester (Erweka TB-24, Germany) and friability tester (Erweka TA3R, Germany were the equipment used).

Standard Calibration Curve for Tramadol HCl

The standard regression equation for tramadol HCl obtained was y = 5.6801x + 0.0085 with a coefficient of regression (R^2) of 0.9998.

Drug/polymer compatibility study

Compatibility study was carried out to determine compatibility between tramadol HCL (TH) and Carbopol 974P and 934 polymers. Briefly, the drug and polymer were thoroughly mixed in a vertex mixer in D:P of 1:1, and then dissolved in phosphate buffer (pH 7.4). Samples were collected after 15 min and analysed spectrophotometrically at 270 nm for drug content. Any colour change was also inspected visually. Thereafter, the drug and polymers were mixed in the same ratio (1:1) and dissolved in water in glass vials and stored at 50 ^{o}C for 2 weeks [8,9]. After two weeks, samples were taken from the physical mixtures and again analysed visually for any change in colour and also analysed spectrophotometericaly for drug content.

Formulation and tablet preparation

Tablets of TH were prepared by direct compression method. The batch size of each formulation was 100 tablets. Table 1 shows the composition of the formulations. Lactose was used as a filler and magnesium stearate as lubricant. All the ingredients, except magnesium stearate, were blended geometrically in pestle and mortar for 10 min and then passed through 1 mm aperture sieve thrice for uniform distribution of the ingredients. Magnesium stearate was added and again passed through the sieve. The mixture was compressed into tablets (compressing weight, 200 mg) in a single punch tablet machine (Erweka AR-400 Germany) fitted with 8 mm round concave punches.

Physicochemical characterization of the tablets

These tests were carried out according to USP [10], as appropriate. Dimensional tests (thickness and diameter) were performed with the aid of Vernier calliper [11]. Weight variation test was performed on 20 tablets from each batch with an electronic weighing balance and the mean taken. Hardness test was performed with a hardness tester (Erweka TB24, Germany) on the 10 tablets from each batch and the mean taken. Friability test was carried out on 20 tablets using a friability tester (Erweka TA3R, Germany) rotating at 25 rpm for 4 min and the mean loss of weight determined.

In vitro dissolution studies

With the aid of Pharmatest dissolution apparatus (D-6312, Hainburg), *in vitro* dissolution studies were conducted using USP Method-I. Potassium phosphate buffer (900 ml, pH 7.4) was used as dissolution medium at 37 ±1 ^{o}C and the speed of the rotating baskets was 100 rpm. Samples (5 ml) were taken at various time intervals and analysed spectrophotometrically at 270 nm after filtering through a 0.45 µ filter. Percent drug release was calculated.

Drug release kinetics

By plotting the fraction release verses time, the drug release kinetics was determined by fitting the data to kinetic models as in Eqs 1 – 5 [12-14]

Table 1: Composition of 200 mg tramadol HCl/Carbopol matrix tablets

	Form.	D:P Ratio	Tramadol HCl	Polymer	Filler (Lactose)	Lubricant (0.5% Mag. stearate)	Co-excipient (filler)
TH/Carbopol tablets without co-excepients							
Carbopol 974P	F1	10:3	100mg	30 mg	69 mg	1mg	
	F2	10:4	100mg	40 mg	59 mg	1mg	
	F3	10:5	100mg	50 mg	49 mg	1mg	
	F4	10:6	100mg	60 mg	39 mg	1mg	
	F5	10:7	100mg	70 mg	29 mg	1mg	
Carbopol 934	F6	10:3	100mg	30 mg	69 mg	1mg	
	F7	10:4	100mg	40 mg	59 mg	1mg	
	F8	10:5	100mg	50 mg	49 mg	1mg	
	F9	10:6	100mg	60 mg	39 mg	1mg	
	F10	10:7	100mg	70 mg	29 mg	1mg	
TH-Carbopol Tablets with co-excipients (CMC, HPMC and starch)							
Carbopol 974P	F11	10:4	100mg	40 mg	41.3 mg	1mg	17.7mg
Carbopol 934	F12	10:4	100mg	40 mg	41.3 mg	1mg	17.7mg

Zero order: $W = K_1t$ (1)
First order: $\ln (100 - W) = \ln 100 - K_2t$ (2)
Higuchi: $W = K_4 t^{1/2}$ (3)
Hixson Crowell: $(100 - W)^{1/3} = 100^{1/3} - K_3t$ (4)
Korsmeyer-Pappas: $M_t / M\infty = K_5t^n$ (5)

where W = the amount of drug release at time, t, k_1 = the zero-order release rate constant, k_2 = the first order release rate constant, k_3 = a constant incorporating the surface volume relationship, k_4 = Higuchi dissolution rate constant, k_5 = kinetic constant compromising the structural and geometric characteristics of the device, n = the diffusion exponent for drug release, and M_t / M_∞ = the fraction of drug release at time, t

Korsmeyer-Peppas equation, which showed the best-fit, was selected, with the fractional drug release into the dissolution medium shown by $M_t / M\infty$. *K* is the constant which is the property of the drug delivery system, and *n* is the diffusional exponent which shows the drug release mechanism, i.e., when n = 0.5, then the drug is released from the matrix tablet with a quasi-Fickian mechanism; when *n* > 0.5, then anomalous, non-Fickian release mechanism exists, and when *n* = 1, then non-Fickian, Case II or Zero order release mechanism exists.

Determination of similarity factor (f_2)

For comparison of the *in vitro* dissolution profiles of two drug formulations, one being the test drug and other the reference standard, Food and Drug Agency (FDA) and Committee for Proprietary Medicinal Products (CPMP) adopted similarity factor (f_2). Its value ranges from 50 - 100. Values < 50 show dissimilarity while values > 50 indicate similarity in *in vitro* release drug profile [16,17]. f_2 was determined as in Eq 6.

$$f_2 = 50\text{Log}\{[1+1/n\, W_t \sum^{n}_{t=1} (R_t-T_t)^2]^{-0.5} \times 100\} \quad (6)$$

where n is pull point, W_t is an optional weight factor, R_t the reference release profile at point, t, and T_t the test release profile at point, t.

Statistical analysis

For statistical significance, one-way ANOVA at $p < 0.05$ was conducted for the release profile using SPSS version 12.0.

RESULTS

No change in colour of the physical mixtures of the drug and polymers were observed even after two weeks of storage. No change in drug content was also observed. The drug content of the drug/carbopol 974P was 99.12 ± 1.17 and 99.32 ± 1.93 before and after 2 weeks, respectively and for the physical mixture containing carbopol 934, it was 100.23 ±1.89 and 100.32 ±1.11 respectively. Compatibility results showed that there was no incompatibility between the drug and the polymers which means the polymers can be used as matrix materials for the preparation of controlled release matrix tablets of tramadol HCl.

Tablet characteristics

Mean tablet was in the range 198 - 203 ± 0.15 mg, indicating good uniformity of weight [11]. Tablet hardness was 6.60 ± 0.10 to 7.80 ± 0.08 kg/cm^2 which is within the recommended USP range of 5 – 10 kg/cm^2. Thickness and diameter were 2.60 ± 0.05 and 8.00 ± 0.07mm, respectively which are within the acceptable USP range of 2 - 4mm and 4 – 13 mm, respectively. Desirable friability limit is < 0.8 % while the tablets obtained exhibited friability in the range of 0.22 ± 0.08 to 0.32 ± 0.04 %.

Table 2: Hardness and friability of tramadol formulations

Polymer	Formulation	Hardness (kg/cm^2)	Friability (%)
Carbopol 974P	F2	7.23 ± 0.11	0.22 ± 0.08
	F3	6.60 ± 0.10	0.28 ± 0.10
	F4	6.94 ± 0.07	0.32 ± 0.04
Carbopol 934	F7	7.80 ± 0.08	0.25 ± 0.03
	F8	7.45 ± 0.15	0.30 ± 0.03
	F9	6.99 ± 0.05	0.23 ± 0.09

Table 3: Kinetic release data for selected formulations

	Formulation	D:P Ratio	Zero Order	First Order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas
Carb 974 P	F2	10:4	0.932	0.945	0.954	0.932	0.976
	F3	10:5	0.964	0.956	0.946	0.933	0.987
	F4	10:6	0.921	0.944	9.935	0.956	0.988
Carb 934	F7	10:4	0.934	0.945	0.967	0.930	0.977
	F8	10:5	0.966	0.957	0.946	0.931	0.984
	F9	10:6	0.922	0.942	0.964	0.952	0.983

In vitro drug release

Drug release data are shown in Figs 1 and 2. As the proportion of polymer increased drug release delayed.

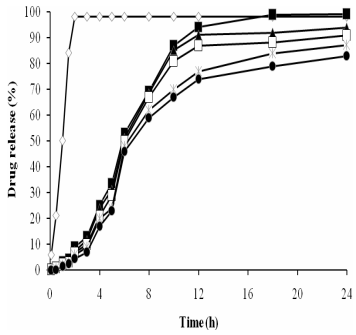

Fig 1: Drug release tramadol tablets containing Carbapol 974P. ***Key:*** ■ = F1, ▲ = F2, □ = F3, x = F4, anf ● = F5, compared standard (◊); n = 3

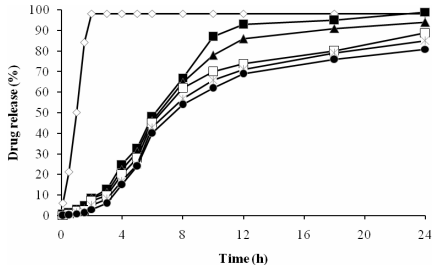

Fig 2: Drug release tramadol tablets containing Carbapol 974P. ***Key:*** ■ = F5, ▲ = F6, □ = F7, x = F8, anf ● = F9, compared standard (◊); n = 3

Influence of co-excipients

Figure 3 shows the effect of starch, CMC and HPMC, used as co-excepeints, on tramdol CR tablets containing either Carbopol 974P or 934. The drug to polymer

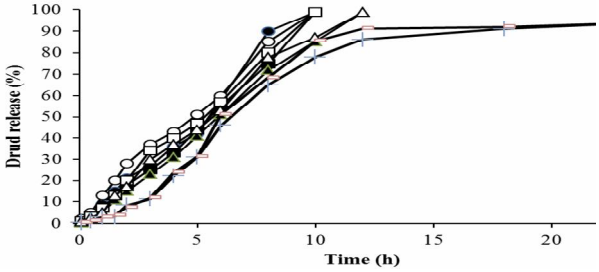

Fig 3: Drug release profiles of tramadol tablets. ***Key:*** Carbopol 974P = ▬, Carbopol 934 = + ▲= HPMC + 974P, ∆ = HPMC + 934, ■ = starch + 974P, □ = starch + 934, ● = CMC + 974P, ○ = CMC + 934 (mean n = 3)

Release kinetics

The results are shown in Table 2. The n value for formulations F2, F3 and F4 were 0.976, 0.987 and 0.988 respectively and those for F4, F5 and F6 were 0.977, 0.984 and 0.983 respectively Korsmeyer-Peppas kinetic model showed the best fitting for the formulations [17].

Similarity factor

The similarity factor (f2) for F2, F3 and F4 was 35.9, 34.7 and 31.8, respectively, while for formulations F7, F8 and F9, it was 36.8, 33.5, and 31.5, respectively. Thus, the release drug profiles of the test formulations were different from that of the reference standard.

DISCUSSION

All the physicochemical data obtained were within acceptable official ranges, and hence the tablets can be further investigated for tramadol release.

As the concentration of Carbopol increased, less drug was released from the polymer. This may be due to hydration of the polymer matrix as it it swells on contact with water and thus closes up the microspores in the swollen tablet, causing a decrease in drug release from the tablet [5]. Furthermore, increase in the amount of the carbomer resulted not only in a reduction of drug release rate but linearization of the drug release curve, leading to a shift towards a swelling-controlled mechanism.

An additional factor may be a reduction in the region of low microviscosity in the swollen tablet. The swelling of a tablet due to polymer hydration results in a rapid decrease in its glass transition temperature (Tg). Microscopically, there is a relaxation of the polymer chains due to stresses introduced by the presence of the dissolution medium which results in an increase in the radius of gyration and end-to-end distances of the polymer chains [5,18]. The resulting increase in the molecular volume of the hydrated polymer reduces free volume due to the presence of the microspores. This effect may manifest as a shift in drug release mechanism [19-21].

In tablets containing co-excipients, the drug was released from the polymer in a shorter time and nearly maximum release was shown after 12 h. Starch is insoluble in water. Insoluble solids may produce non-uniformity in the polymeric membrane around the drug, causing imperfection in the membrane, leading to quick release of drug from the tablets. Starch is water swellable and could have caused rupture of the polymeric membrane, and increase in drug release rates. Our findings in respect of the influence of starch are in agreement with those of Khan & Zhu [5] and Shefaat *et al* [22].

CMC, a water soluble polymer, also enhanced the release rate of tramadol HCl from the tablets and thus confirms the findings of Khan & Zhu [23] and Shefaat *et al* [22] that water-soluble co-excipients can create osmotic forces that may break up membranous barriers, resulting in higher release rate. The effect of inclusion of HPMC, also a water soluble polymer, was similar to that of CMC, and the same mechanism applies [5,22].

The value of the diffusion coefficient (n) in the Korsmeyer-Peppas model being > 0.5 for all the CR formulations, indicates that drug transport mechanism was anomalous, non-Fickian diffusion. The f_2 data further lend support to the fact that the test formulations developed are controlled-release.

CONCLUSION

The tablets developed showed good physicochemical properties and demonstrated satisfactory controlled drug release. Thus, Carbopol 974P and 934 are suitable drug release rate-controlling polymers for tramadol and possibly similarly water soluble polymers.

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