International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.2, No.4, pp 2506-2511, Oct-Dec 2010

Effect of Solubility of the Drug on the release Kinetics from Hydrophilic Matrices

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Abstract: The purpose of the present study was to observe the effect of drug solubility on the release kinetics of water soluble tramadol hydrochloride and insoluble aceclofenac from hydrophilic polymer (hydroxypropyl methylcellulose) based matrix formulations. Matrix tablets were prepared by wet granulation method. The prepared tablets were analyzed to determine their hardness, friability, weight variation, drug content and *in vitro* drug release. Mechanism of drug release from the tablets having soluble drug was found that anomalous non-Fickian diffusion transport where as insoluble drug showed zero-order release. Matrices having water soluble drug showed low t_{50}% value than the insoluble drug formulations. T-test pointed to a significant difference in amount of both drugs released due to the difference in solubility. Solubility of drug effects kinetics and the mechanism of drug release.
Key words: Tramadol hydrochloride, aceclofenac, matrix tablets, solubility, release kinetics.

INTRODUCTION

The therapeutic success of drugs having short biological half life than the duration of ailment depends on maintenance of optimum blood drug levels with minimal fluctuation through out the period[1]. One such product, which have gained prominence in the treatment of pain management are sustained release formulations. One of the most commonly used methods of modulating tablet drug release is to include it in a matrix system. The classification of matrix system is based on the matrix structure, release kinetics, controlled release properties on the chemical nature and properties of employed materials[2]. Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, do not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier which controls the drug release form and the liquid penetration in the centre of the matrix system[3]. Successful formulation of a hydrophilic matrix depends on various factors such as formulation components like active ingredient, hydrophilic polymer, excipients; various manufacturing aspects such as granulation, direct compression; tablet properties (hardness, friability, shape, size), coatings[4].

In the present investigation, one of the important aspects of hydrophilic matrix ER formulations, namely effect of solubility of drug on the release was studied. To perform this work drug from two different BCS classes were selected, namely tramadol hydrochloride and aceclofenac.

Tramadol is Tramadol hydrochloride (TRH), a synthetic opoid of the aminocyclohexanol group, which is used in the treatment of osteoarthritis when NSAIDs like acetaminophen, or COX-2 inhibitors alone produce inadequate pain relief. It is a centrally acting analgesic with weak opoid agonist properties. The half-life of a drug is about 5.5 hrs and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hrs with a maximum dosage of 400 mg/day. To reduce the frequency of administration and to improve patient compliance, a sustained release formulation of tramadol is required[5-7].

Aceclofenac (ACF) is a non-steroidal drug having potent analgesic, anti-inflammatory and antipyretic activities due to its prostaglandin

synthatase inhibitory action. It is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after oral dose. The plasma elimination half-life of the drug is approximately 4h and dosing frequency 2-3 times daily with dose range 100-200 mg, which causes adverse effects to GIT[8]. To improve the therapeutic efficacy of aceclofenac and reduce the severity of upper GI tract side effects a dosage form with modified release properties should be prepared.

MATERIALS AND METHODS

Materials

TRH was obtained as a gift sample from Aurobindo Pharma Ltd., Hyderabad; ACF was obtained as gift sample from Dr. Reddy's laboratories, Hyderabad. Hydroxy propyl methylcellulose K100M (HPMC), lactose, calcium carbonate, starch, polyvinyl pyrrolidone (PVP) K-30, magnesium stearate and talc were procured commercially. All other ingredients are analytical grade.

Preparation of matrix tablets

Matrix tablets were prepared by wet granulation method as reported by Bettini *et al* [9] using PVP K-30 as binder, alcohol as wetting agent and lactose as diluent. Granules of both drugs aceclofenac and tramadol hydrochloride were prepared and blended with talc and Magnesium stearate used as lubricant in a ratio of 2:1. The blend was compressed using Cadmach tablet compression machine, equipped with beveled 8 mm flat-faced punches producing matrix tablets to a hardness of 4-6 Kg/ Sq.cm. Under the same conditions all the tablets containing ACH and TRH were prepared and the formulation details are given Table 1.

Tablet assay and physical evaluation[10, 11]:

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a hand operated Monsanto hardness tester (India). Friability of the tablets was determined in a Roche friabilator. The thickness of the tablets was measured by vernier callipers. Weight variation was performed according to the official method. Drug content of tramadol hydrochloride and aceclofenac was carried out by measuring the absorbance of the sample at 271 nm and at 273 nm respectively using UV-spectrophotometer.

Dissolution studies:

Drug release studies of tablets were performed using USP dissolution rate test apparatus (Apparatus 2, 50 rpm, 37±0.5^{o}). Study was performed first 2 hours in pH 1.2 buffer (900 mL) and the remaining time in pH 7.4 phosphate buffer (900 mL) [12, 13]. Thus, the dissolution testing conditions were representing same as that of simulated gastric and intestinal juices without enzymes. A 5 mL aliquot was withdrawn at different time intervals, filtered (through 0.45µ) and replaced with 5 mL of fresh dissolution medium. Amount of drug present in the sample was determined by UV spectroscopy at 271 nm, 273 nm for tramadol hydrochloride and aceclofenac respectively, after suitable dilution of the sample. The dissolution experiments were conducted in triplicate.

Kinetics of Drug Release

To study the mechanism of drug release from the matrix tablets the release data were fitted to zero-order, first-order, and Higuchi equation [14]. These models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation)[15], which is often used to describe the drug release behavior from polymeric systems.

$$\text{Log } (M_t / M_f) = \text{Log } k + n \text{ Log } t \longrightarrow (1)$$

Where, M_t is the amount of drug release at time t, M_f is the amount of drug release after infinite time, k is a release rate constant incorporating structural and geometric characteristics of the tablet and 'n' is the diffusional exponent indicative of the mechanism of drug release. To clarify the release exponent for different batches of matrix tablet, the log value of percentage drug dissolved was plotted against log time for each batch. A value of n = 0.45 indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release [16].

Statistical analysis

In vitro drug release data of different formulations of TRH and ACF were subjected to the one-way ANOVA to find out whether there was any significant difference between the formulations. Statistical analysis of the data was performed using the PRISM software (Graphpad, USA). A t-test was performed to find out if there was any significant difference in the release pattern of two drugs, TRH and ACF (F1 and F4) having same diluents (lactose).

Table 1: Composition of sustained release matrix tablets of TRH and ACF

Ingredients	F1	F2	F3	F4	F5	F6
Tramadol hydrochloride	100	100	100	-	-	-
Aceclofenac	-	-	-	200	200	200
Lactose (mg)	66	56	46	53	38	23
HPMC (mg)	20	30	40	30	45	60
PVP K30 (mg)	8	8	8	8	8	8
Magnesium stearate (mg)	2	2	2	3	3	3
Talc (mg)	4	4	4	6	6	6
Total weight (mg)	200	200	200	300	300	300

RESULTS AND DISCUSSION

The matrix tablets were prepared by wet granulation method according to the formula given in Table 1. The prepared tablets were evaluated for hardness, friability, content uniformity, uniformity of weight and *in vitro* drug release studies. Hardness of the tablets in all the batches was found to be in the range of 4.6 to 5.5 kg/cm^2. Friability of the tablets was in the range of 0.39-0.81%. Drug content was found to be uniform for all the batches of tablets prepared and was found to be with in 100 ± 2% of labeled claim. The thickness of the tablets ranged from 3.7-4.6 mm. The values of hardness and friability indicate good handling property of the prepared matrix tablets. The prepared matrix tablets were subjected to *in vitro* drug release studies using 0.1N HCl for 2h, after that in phosphate buffer pH 7.2. The effect of polymer concentraiton on the release of water soluble TRH and water insoluble ACF was studied for tablets containing 10, 15 and 20% HPMC K100. Figure 1 and 2 depicts how the amount of HPMC affects the release of both drugs. The release rate was found to be decreasing as the concentration of polymer increased from 10 to 20 %. Formulations containing water soluble drug showed a rapid release in the first hour. This phenomenon may be attributed to surface erosion and initial disaggregation of the matrix tablet, which occurs due to formation of the gel layer around the tablet core. Water soluble tramadol hydrochloride formulations F1, F2 and F3 were able to sustain the drug release for 7 (94.36%), 9 (95.63%) and 11 (89.63%) hours respectively. Water insoluble aceclofenac formulations F4, F5 and F6 were able to sustain the drug release for 9 (93.63%), 9 (91.23%) and 12 (84.32%) hours respectively. In the case of formulation F7, 15%of HPMC was sufficient to sustain the drug release for 12 hours. On increasing the concentration of HPMC up to 20%, the release of the drug was slow and only 84.32% after 12 hours. It was observed that when the polymer concentration was increased, the drug release rate decreased. This is due to the lower degree of the swelling because of higher concentration of polymers. However, further increase in the polymer concentration did not significantly affect the drug release rate. Water insoluble drug required a smaller amount of polymer to sustain the release compare to the water soluble drug because the hydrophobic nature of the drug restricts the penetration of the solvent inside the matrix, which retarded drug release from the matrix.

Table 2: Properties of matrix tablets of TRH and ACF

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	3.7±0.45	4.6± 0.56	0.75	199±2.5	99.5 ± 0.8
F2	3.8±0.52	5.4± 0.53	0.81	201±1.6	100.8 ± 2.1
F3	3.8±0.31	4.9± 0.98	0.79	202±0.98	99.7± 3.2
F4	4.4±0.54	5.5± 0.52	0.68	298±1.65	99.8 ± 0.9
F5	4.4±0.37	4.8± 0.57	0.54	302±1.54	101.9 ± 2.4
F6	4.5±0.46	5.2± 0.39	0.39	303±0.24	99.6 ± 2.3
T1	3.8±0.23	5.2± 0.77	0.51	202±0.57	98.3± 1.9
A1	4.6±0.41	4.9± 0.56	0.48	303±1.29	101.1± 0.9

T1 is commercial tramadol tablet, A1 is commercial aceclofenac tablet

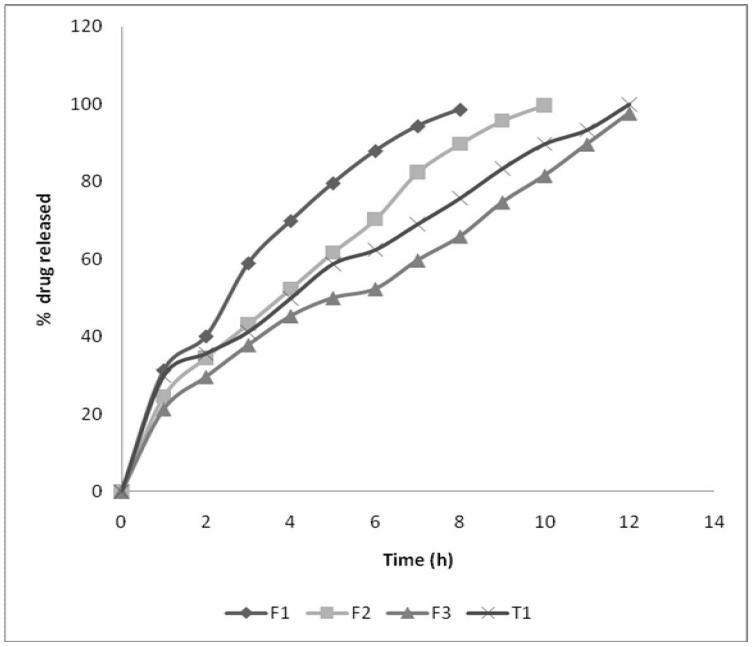

Figure 1: *In vitro* drug release data from the tramadol hydrochloride formulations

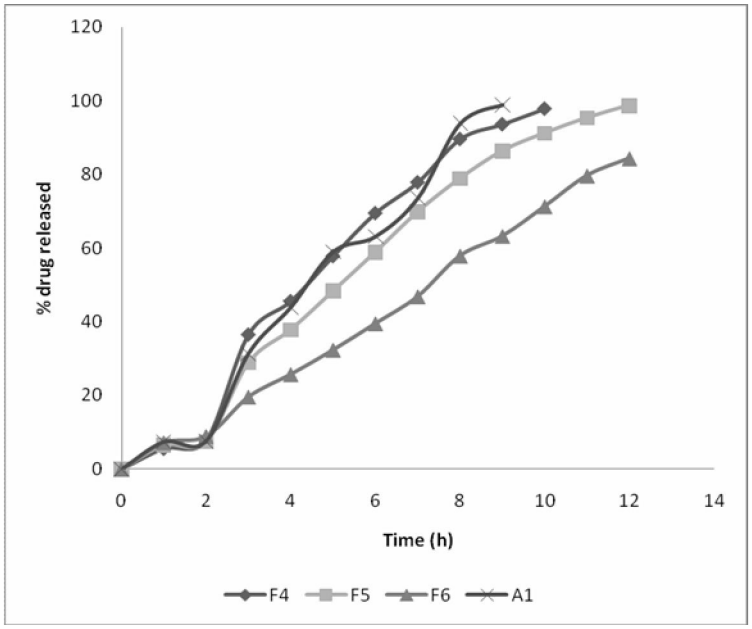

Figure 2: *In vitro* drug release data from the aceclofenac formulations

Table 3: Kinetics of drug release from matrix tablets of TRH and ACF

Formulation	Drug release kinetics (r)				Release exponent
	Zero order	First order	Higuchi	Korsmeyer	
F1	0.949	0.962	0.9764	0.9841	0.4005
F2	0.9280	0.938	0.9738	0.9836	0.3663
F3	0.9164	0.9790	0.9702	0.9824	0.3559
F4	0.989	0.946	0.9000	0.8912	0.924
F5	0.996	0.930	0.9190	0.9260	0.975
F6	0.994	0.947	0.9167	0.9157	1.0423
T1	0.978	0.935	0.9882	0.9967	0.4603
A1	0.989	0.868	0.8574	0.9283	1.0782

From formulations F1 to F3 29 – 40% of tramadol was released within two hours of the dissolution study whereas from formulations F4-F6 showed 7-9 % of aceclofenac release, means no burst release was observed. By using the same polymer concentration, the drug release of both drugs varied due to the solubility differences that allowed rapid disintegration of the polymeric layer and faster release of the drug. The soluble drug showed rapid release compared to the insoluble drug, it can be observed from the Figure 3. The release kinetic data is given in Table 3. The kinetic data of the formulations F1 to F3 and T1 showed good fit in the Korsmeyer-Peppas model (0.982-0.9964), where as formulations F4 to F6 and A1 showed high linearity with the zero-order equation (0.989-0.994). The release exponent value 'n' for the tramadol hydrochloride formulations ranged from 0.3559-0.4603, for the aceclofenac formulations was ranged from 0.924-1.0782. From the data, it can be suggested that the mechanism that led to the release of tramadol hydrochloride was an anomalous non-Fickian diffusion transport, which indicates that the drug release occurred through diffusion in the hydrated matrix and polymer relaxation. In case of aceclofenac, the mechanism of drug release shifted from anomalous non-Fickian diffusion to swelling controlled dug delivery systems with zero-order kinetics. The marketed formulations also showing same type of release mechanism.

CONCLUSION

Tramadol hydrochloride and aceclofenac sustained release matrix tablets were prepared successfully using HPMC as matrixing agent. The results of present study demonstrate that release retarding efficiency of HPMC at different concentrations significantly depends on the solubility of drugs. From this study, it is observed that ACF released in much lesser extent than TRH from matrix tablets containing same amount of HPMC. The mechanism of drug release followed anomalous non-Fickian diffusion transport and zero-order for water soluble and insoluble drugs respectively.

ACKNOWLEDGEMENTS

The authors are thankful to Chalapathi Educational Society, Guntur for providing the necessary facilities.

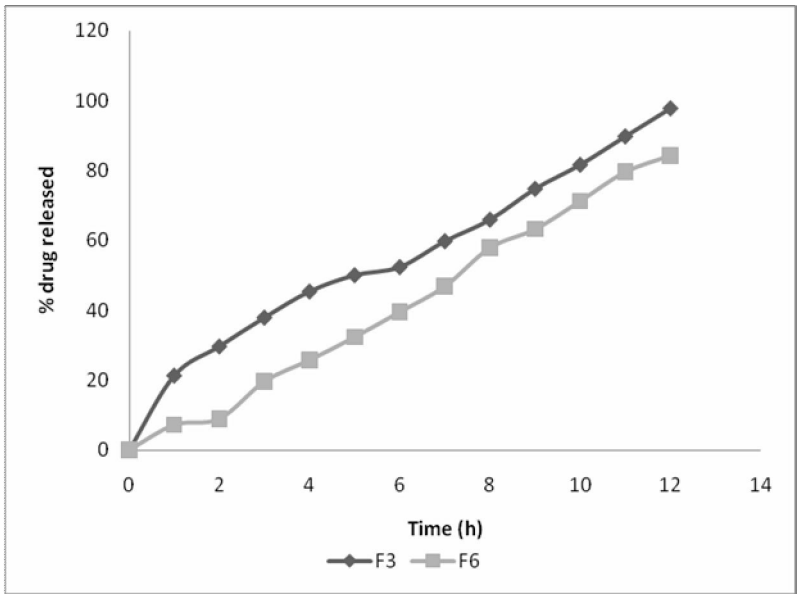

Figure 3: Comparative drug release (ACF and TRH) from matrix tablets containing same amount of polymer

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