In vitro Release Study of Ketorolac from Extended Release Capsules Filled with Semisolid Matrix of Glyceryl Esters of Fatty Acids

Armin Minhaz[1], Md. Saiful Islam[2], Md. Habibur Rahman[2] and Reza-ul Jalil[2]*

[1] Department of Pharmacy, The University of Asia Pacific, Dhanmondi R/A, Dhaka 1205, Bangladesh
[2] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka 1000, Bangladesh

Abstract

Three semisolid fill bases were selected for the formulation of 12 capsule formulations, each containing 30mg of Ketorolac tromethamine (KT). The fill materials were selected based on their matrix forming property after heating. The fill matrices included lipophilic bases (glyceryl monostearate-GMS, glyceryl palmitostearate-GPS, and glyceryl dibehenate-GB), soybean oil and Ketorolac tromethamine. Semisolid matrixes of Ketorolac were prepared by melt-matrix method and were filled in hard gelatin capsule shell (size 2). The dissolution study indicated that formulations containing GPS and GB bases showed the best release profiles. These are F5 (55% GPS-15% KT); F6 (65% GPS-15% KT); F7 (75% GPS-15% KT); F8 (85% GPS-15% KT), and F10 (65% GB-15% KT). Release data indicated slower release rates of GB based formulations (F9 to F12). For instance, the extent of drug release at first 1 hour was 44% and after 8 hour was 71% for 85% level of GB (F12). In conclusion, the pharmaceutical quality of Ketorolac tromethamine capsules can be improved by using a semisolid lipophilic matrix filled in hard gelatin capsules.

Keywords: Melt-matrix, Ketorolac tromethamine, Glyceryl monostearate, Glyceryl palmitostearate, Glyceryl dibehenate, Hard gelatin capsule shell.

Introduction

Filling hard gelatin capsules with semisolid matrices (SSM) is a simple technique that has been used to extend the release of many drugs and obviates the need for additional excipients, granulation, and compression steps (Galal *et al.* 2004). It also offers many advantages including improvement in chemical stability, excellent homogeneity and content uniformity, easier formulation of oily drug, and preparation of oral sustained release formulations (Wu *et al.* 2002). The cost of lipid matrices is also relatively little to produce, and in some cases, it is possible to minimize the influence of physiological variables on drug release (Esquisabel *et al.* 1996).

Interest in liquid and semisolid matrix (SSM) filling of hard gelatin capsules was renewed in the late 1970s (Walker *et al.* 1980). Recent decades have seen substantial advances in the use of new excipient mixtures for the filling of hard gelatin capsules and in the technology of their manufacture. Such advances have involved both the filling equipment and the design and sealing of the gelatin shells (Eisberg 1981; Jones 1987).

SSM capsule formulations offer many advantages over conventional powder filled systems. These include excellent fill weight and content uniformity, the elimination of dust or cross contamination, easier formulation of oily drugs, improved drug stability and easy modification of drug release rate (Somerville *et al.* 1984; Doelker *et al.* 1986; Bowtle *et al.* 1988; Naidoo 1989; Baykara and Yuksel, 1991).

Ketorolac tromethamine (KT) was the model drug in this study which was incorporated in lipid-based semisolid matrix systems to extend the release of it. Three fatty esters namely glyceryl monostearate, glyceryl palmitostearate and glyceryl dibehenate were used as the matrix former.

Experimental

Materials

Ketorolac tromethamine was a generous gift from Zydus Cedila (Cedila Healthcare LTD, INDIA).

*** Author for Correspondence:** Reza-ul Jalil, Professor, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka 1000, Bangladesh. Email: raju1559@yahoo.com

Glyceryl monostearate (Danisco, UK), glyceryl palmitostearate (Precitol®, Gattefosse, France), glyceryl dibehenate (Compritol AT088®, Gattefosse, France) were received from their respective sources.

Preparation of Semisolid Melt-matrix of Ketorolac

Semisolid lipid mixture was prepared by melt-matrix method. At first Ketorolac tromethamine (KT) and lipid excipient were taken accurately and accordingly to table 1 in 5ml glass vials. The vials were then heated around 70-75°C and the mixtures were mixed homogenously with the help of glass rod. In each case, 200mg semisolid matrix was filled in the size 2 hard gelatin capsule shell. In this case, the mixture was withdrawn by a dropper and then filled into the hard gelatin capsule shell by placing the capsule shell die plate on an electronic balance. After solidification of the melt matrix, the capsule shells were stored in an air tight container.

Table 1: Lipid based formulations of Ketorolac Tromethamine

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ketorolac Tromethamine	30	30	30	30	30	30	30	30	30	30	30	30
Glyceryl monostearate	110	130	150	170	-	-	-	-	-	-	-	-
Glyceryl palmitostearate	-	-	-	-	110	130	150	170	-	-	-	-
Glyceryl dibehenate	-	-	-	-	-	-	-	-	110	130	150	170
Soybean Oil	60	40	20	-	60	40	20	-	60	40	20	-

In vitro dissolution study

In vitro dissolution study of semisolid filled capsules of KT was performed in a USP Type III Dissolution Apparatus (Electrolab, India). The study was carried out for 8 hours where paddle speed was set at 50rpm and dissolution media was 900ml distilled water maintaining the temperature at 37 ± 0.5°C. Dissolution samples were withdrawn at predetermined intervals and each time the sink condition was maintained with fresh distilled water. Withdrawn samples were analyzed for drug content by a spectrophotometer (UV mini-1240, Shimadzu Corporation, Japan) at 322nm.

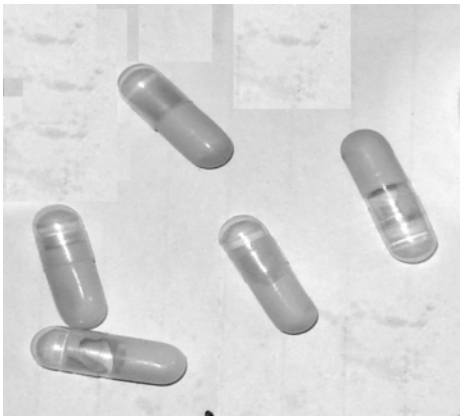

Figure 1: Semisolid matrix of Ketorolac filled in hard gelatin capsule shell.

Results and Discussions

Semisolid mixture of KT by melt-matrix method were successfully prepared and filled in hard gelatin capsule shell (Figure 1). *In vitro* release of KT from semisolid matrix was then studied in distilled water.

Figure 2 shows the release property of KT from the prepared formulations. In case of Figure 2a, release curves of KT are shown from the melt-matrix capsules where glyceryl monostearate (GMS) was used as the matrix former. USPNF 23 describes glyceryl monostearate as consisting of not less than 90% of monoglycerides, chiefly glyceryl monostearate ($C_{21}H_{42}O_4$) and glyceryl monopalmitate ($C_{19}H_{38}O_4$). Glyceryl monostearate is a white to cream-colored, wax like solid in the form of beads, flakes, or powder. It is waxy to the touch and has a slight fatty odor and taste. GMS is a lipophilic emulsifying agent (HLB 3.8) which is practically insoluble in water (Rowe *et al.* 2003). Besides, it is a lubricant for tablet manufacturing and may be used to form sustained release matrices for solid dosage forms (Peh and Yuen,

1995). While this excipient was used at 55% level (F1), 96.23% KT was released after 8 hours of dissolution where nearly 60% drug was found to be released within first 1 hour. As the amount of this excipient was increased gradually, KT release was found to be reduced accordingly (Figure 2a). Release was 92.82% for 65% level of GMS (F2), 88.82% for 75% level of GMS (F3) and 84.82% for 85% level of GMS (F4). It is clearly evident that GMS retarded the release of KT from the melt-matrix capsules. This release retardant activity of GMS was also evident previously (Peri *et al*. 1994).

In Figure 2b, release curves of KT are shown where melt-matrix capsules were prepared with glyceryl palmitostearate (GPS). Similar but more reduced release was observed while GPS was incorporated in the matrix formulation. After incorporation of this excipient, KT release was 98.23% for F5, 97.82% for F6, 87.82% for F7 and 78.8% for F8. That is, like GMS, similar gradual decrease in the drug release with increase in GPS content was observed. GPS is mixture of mono-, di-, and tri-, glycerides of C_{16} and C_{18} fatty acids (Rowe *et al.* 2003). It is also a water insoluble excipient which is used as tablet and capsule lubricant. Due to this lipophilic nature of the GPS, it has been used as a matrix former in sustained release dosage forms (Shaikh *et al*. 1991; Gao *et al.* 1995).

Most extended release of KT was found with glyceryl dibehenate (GB) (Figure 2c). Even at the lower levels of this excipient, comparatively better sustained release curves were found than the previous two excipients. At 55% and 65% level of GB (formula F9 & F10), 94.23% and 88.23% KT was released. But importantly at higher levels of this excipient, most sustained release of KT was observed. At 75% and 85% level of GB (formula F11 & F12), KT release was 82.82% and 71.66% respectively. GB is a mixture of glycerides of fatty acids, mainly behenic acid. It is also practically insoluble in water (Rowe *et al.* 2003). It is a tablet and capsule lubricant also (Abramovici *et al.* 1986). But most importantly, GB has a good release retarding capacity which might play the role in controlling the release of the drug from semisolid matrix (Li *et al*. 2006; Obaidat and Obaidat, 2001; Perez *et al.* 1993). GB has also been used as coating agent for oral sustained-release dosage forms (Faham *et al.* 2000; Hamdani *et al.* 2003).

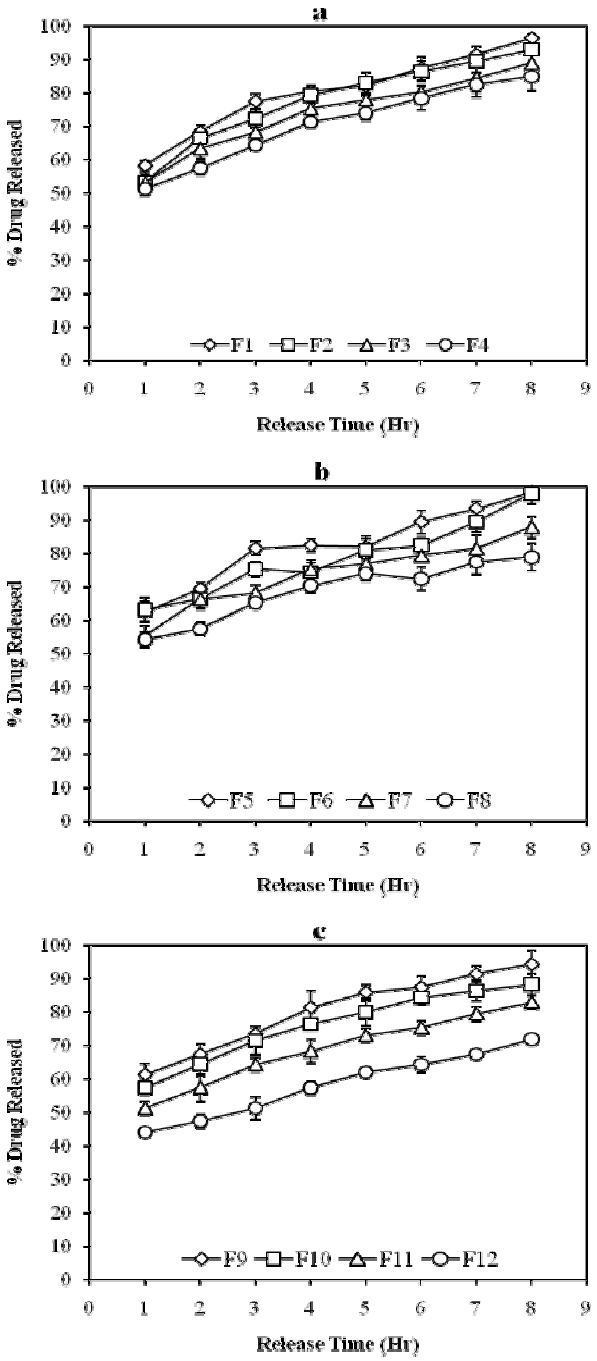

Figure 2: Zero order release of Ketorolac from semisolid melt-matrix prepared using (a) glyceryl monostearate, (b) glyceryl palmitostearate, (c) glyceryl dibehenate (n = 3).

From the figure, it is clearly seen that as the concentration of this excipient was increased from 55% to 85%, drug release was reduced more

prominently compared with other two excipients. Even drug release could be prolonged more with this excipient (Barthelemy *et al.* 1999).

However, in case of all the formulations (F1-F12), sustained release curves were found. In the release curves (Figure 2), it is clearly seen that as the amount of the lipophilic excipients was increased gradually, more and more sustained release nature in the curves were observed accordingly. Especially, glyceryl dibehenate (formula F9 to F12) showed most release retarding capacity amongst all. Lipophilic nature, release retardant property of the excipients attributed to this reduced release of KT from the semisolid matrix. Moreover hindered penetration of the dissolution media inside the semisolid matrix might play an additive role in the slower release of the drug which was actually due to the increased lipophilicity of the matrix system.

Table 2: Kinetic parameters of the release curves

	Glyceryl monostearate				Glyceryl palmitostearate				Glyceryl dibehenate			
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
r^2 (zero)	0.94	0.93	0.95	0.97	0.93	0.95	0.93	0.92	0.96	0.95	0.97	0.99
r^2 (higuchi)	0.98	0.98	0.99	0.99	0.95	0.92	0.96	0.95	0.98	0.99	0.99	0.98
r^2 (first)	0.93	0.96	0.92	0.93	0.88	0.81	0.87	0.82	0.95	0.91	0.90	0.88
MDT (hour)	1.93	2.14	2.69	3.20	1.73	2.19	2.94	4.48	1.93	2.58	3.68	7.21

Table 2 shows different kinetic parameters of the release curves. Kinetic equations of different release model (zero-order, first-order and Higuchi's equation) were applied to interpret the release rate from matrix system. The best fit with higher correlation was found with the Higuchi's equation for almost all the formulations.

To characterize the drug release rate in different experimental conditions, mean dissolution time (MDT) was calculated from dissolution data according to Mockel and Lippold (1993) using the following equation:

$$MDT = (n/n+1).k^{-1/n}$$

where n = release exponent and k = release rate constant.

MDT values are shown in Table 2. In case of GMS comprising formulations, MDT value was 1.93h while 55% level of the excipient was used. This value was 3.2h while 85% excipient was used. Similarly MDT value was 1.73h for 55% of GPS and was 4.48h for 85% of GPS. But GB comprising formulations showed maximum MDT. Especially use of this excipient at 85% level was found to be proved as the most sustained release formula. MDT value of this formula was 7.21h.

To study the release rate of the curves, Higuchi curves were considered and a comparative study among the release rate of the curves from different formulas is shown in Figure 3. As the excipient amount was increased, release rate values were also decreased. Finally at 85% level, release rate values of all three formulations were found smallest. And it clearly indicates the best release retarding capacity of the formulations at this concentration level of the excipients.

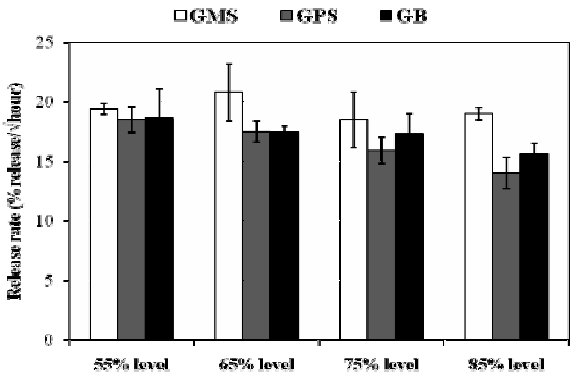

Figure 3: Comparative release rate study of Ketorolac from three glyceryl esters of fatty acids based semisolid matrixes.

Conclusion

The process of melt-matrix preparation was very simple with the glyceryl esters of fatty acids and they were very easily filled inside the hard gelatin

capsules. Semisolid matrix filled capsules were also proved successful in preparing sustained release preparation of Ketorolac tromethamine. Matrixes with glyceryl monostearate, glyceryl palmitostearate and glyceryl dibehenate were all capable to extend the release up to 8 hours. Especially the matrixes with glyceryl palmitostearate and glyceryl dibehenate were proved very successful to obtain better and almost linear release curves for 8 hours. So, this idea of melt-matrix method with glyceryl esters might be considered as an effective technique for preparing sustained release products of water soluble drugs like Ketorolac tromethamine.

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