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Impact of Sodium Lauryl Sulphate on the Release of Carbamazepine from Methocel K15M CR based Matrix Tablets

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Abstract

In the present study, an attempt has been taken to evaluate the effect of water soluble surfactant, sodium lauryl sulphate (SLS) on the release profile of a poorly soluble drug, carbamazepine. Matrix tablets of carbamazepine were prepared by direct compression method using Methocel K15MCR as release controlling polymer. Varying amounts of SLS were used in seven different formulations to observe the impact on the extent of release rate and mechanism of drug release. Avicel PH101, a derivative of microcrystalline cellulose, and magnesium stearate were used as direct compression diluent and lubricant respectively. The dissolution study of carbamazepine from these extended release matrix tablets was conducted for 8 hours using paddle method in 900 ml 0.1N HCl as dissolution medium. The data obtained form the dissolution studies were explored and explained with the help of zero order, Higuchi and Korsmeyer's kinetic equations. It was found that the dissolution rate of carbamazepine was directly proportional to the amount of SLS present in the matrix tablets. The most important finding was the shift of release mechanism due to the incorporation of a solubilizer. In one end where there was no SLS or smaller amount of SLS, the release mechanism was dominated by polymeric erosion and swelling. On the other hand, drug release mechanism was controlled by Fickian diffusion where SLS content was higher. In addition, under the experimental conditions MDT values declined as the surfactant concentration in the tablet matrices was increased. These results clearly demonstrated that the dissolution rate, extent and mechanism of carbamazepine could be manipulated by optimizing the amount of SLS in the tablet formulation.

Key words: Dissolution test, Release kinetics, Carbamazepine, Sodium lauryl sulfate.

Introduction

Developing formulation using dissolution test methods for poorly water-soluble drug products has been an important task to formulation scientists. Problems encountered with poorly water-soluble drug products include a low extent of drug release and a slow release rate. General strategies to enhance their dissolution patterns rely upon either changing the dissolution medium pH, or adding solubilizer such as surfactants and cyclodextrin derivatives into the dissolution medium (Chen *et al*., 2003; Qazi *et al*., 2003; Sun *et al*., 2003; Jain *et al*., 2001; Castillo *et al*., 1999; Crison *et al*., 1997; Shah *et al*., 1989; Aunins *et al*., 1985; Serajuddin *et al*., 1984). In rare cases, when the above attempts turn out to be unsuccessful, non-aqueous solvents are added into a dissolution medium. Despite having some health hazards, the use of surfactants in the tablet and capsule formulations for *in vitro* dissolution testing of water insoluble drugs has increased because of their mechanistic similarities to *in vivo* dissolution. Types of surfactnts that are used in the dosage form to increase the dissolution include polysorbate 20/80, cetyltrimethylammonium bromide, sodium lauryl sulfate (SLS), lecithin, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium oleate, and sodium glycocholate. Among these, SLS has been proven as the agent of choice because it is inexpensive and it possesses good solubilizing capacity at relatively low concentrations. Already, several authors reported that SLS could enhance dissolution of poorly water-soluble compounds (Sun *et al*., 2003; Qazi *et al*., 2003; Crison *et al*., 1997; Shah *et al*., 1989). Moreover, the findings of a lot of investigations showed that the presence of surfactant infulenced the tablet disintegration rate, producing a finer dispersion of disintergrated particles with correspondingly larger surface area for drug dissolution.

Materials and Methods

Carbamazepine, active ingredient in this study, was a gift sample from Square Pharmaceuticals Bangladesh

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Limited. Sodium lauryl sulphate (SLS) is the excipient under investigation was used for its wetting ability and also for its capability to increase the solubility of poorly soluble drugs. Methocel K15MCR which is one of the most commonly used polymers in the preparation of matrix tablets was used as release retardant. Avicel PH101 was used as a direct compression diluent and also for its excellent binding and disintegration property.

The active ingredient and other excipients were accurately weighted for thirty tablets according to the formulations and blended in a laboratory designed with small drum blender for 30 minutes. Particular attention has been given to ensure thorough mixing and phase homogenization. The appropriate amounts of mixture were accurately weighted in an electronic balance for the preparation of each tablet and finally compressed using a Perkin-Elmer laboratory hydraulic press.

Carbamazepine release from matrix tablets was determined by using USP XXII Dissolution Tester. The dissolution test was performed with 900 ml 0.1N HCl at 37° ± 0.5ºC and 75 r.p.m. The absorbance of the solutions was measured at 285 nm for drug carbamazepine by using a Shimadzu UV-1201 UV/Visible double beam spectrophotometer (Shimadzu, Japan). Percentage of drug released was calculated by using an equation obtained from the standard curve. The dissolution study was continued for 8 hours to get a simulated picture of the drug release in the *in vivo* condition and drug dissolved at specified time periods was plotted as percent release versus time (hours) curve. This drug release profiles were fitted to several mathematical models to get an idea about the release profile of carbamazepine from the matrix tablets.

Quantitative approach to explore drug release: After completing *in vitro* dissolution of all the batches for eight hours, the data was treated with zero order and Higuchi equations (equations 1 and 2 respectively).

$$M_t = M_0 + k_0 t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

$$M_t = M_0 - k_H t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

In these equations, M_t is the cumulative amount of drug released at any specified time (t) and M_0 is the dose of the drug incorporated in the delivery system, k_0 and k_H are rate constants for zero order and Higuchi model, respectively. 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 well-known Korsmeyer kinetic equation to ascertain the mechanism of drug release.

$$\log (M_t/M_\infty) = \log k + n \log t \quad \ldots\ldots\ldots\ldots\ldots (3)$$

Where, M_∞ is the amount of drug released after infinite time; k is the release rate constant which considers structural and geometric characteristics of the tablet, n is the diffusional exponent or release exponent and t is the time, indicative of the mechanism of drug release. For a tablet having cylindrical shape, when n is bellow 0.45, the Fickian diffusion phenomenon dominates, and n between 0.45 and 0.89 is an anomalous transport (non-Fickian diffusion), often termed as first-order release. After the n value reaches 0.89 and above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is termed as zero-order. In this case, the drug release is dominated by the erosion and swelling of the polymer. Value of release exponent (n), obtained from Korsmeyer equation, was used to calculate Mean Dissolution Time (MDT), using the following equation:

$$MDT = \left(\frac{n}{n+1}\right) k^{-1/n}$$

Results and Discussion

Matrix tablets were prepared according to the formulations stated in Table 1 with carbamazepine as the active ingredient, sodium lauryl sulfate (SLS) as release modifier and Methocel K15MCR as release retardant. Formulations (formulation-1, formulation-2, formulation-3, formulation-4, formulation-5, formulation-6 and formulation-7) of carbamazepine were prepared. The amount of drug and Methocel K4MCR in each formulation was kept constant and the amount of SLS was increased gradually where formulation-1 did not contain SLS. Formulation-1 to formulation-7 were compared (Figure 1) to evaluate the change of release profile due to the change of the amount of SLS.

From the zero order release profile it was observed that the total percent release of drug from formulation-1 to formulation-7 were 33.7%, 35.2%, 38.8%, 42.5%, 48.9%, 52.4% and 55.1%, respectively which was indicated that the total percent release and zero order release rate constant of carbamazepine from different formulations were increased due to increase sodium lauryl sulphate (SLS) content in the formulations (Table 2). First three formulations which contained no (formulation-1) or relatively less quantity of SLS (formulation-2 and

formulation-3) showed better following tendency of korsmeyer release kinetics as suggested by their R-squared values which were 0.998, 0.982 and 0.985, repcetively obtained from Korsmeyer release equation. Whereas formulation-4 (R^2=0.992), formulation-5 (R^2=0.984) and formulation-7 (R^2=0.994) best fitted with Higuchi release model. But formulation-6 (R^2=0.989) again followed Korsmeyer release pattern (Table 2). From figure 1 it is also clear that formulation-1 which contained no surfactant showed most predictable and linear pattern of drug release with minimum fluctuations. But when SLS was incorporated in matrix tablets the release patterns became to some extent aberrant which is also supported by the values of standard deviations and R-squared values of different formulations (Table 2). Higuchi release rate also displayed a gradual increase with the increase of the amount of SLS, but R-squared value of Higuchi release kinetics showed no trend with the change of SLS level. Another observation was that with the increase of SLS, formulations deviated to follow the zero order kinetics which was proved by the R^2 values obtained from zero order equation. However, formulation-7 did not comply with this trend.

Kinetic study of drug release by zero order and Higuchi equation can provide very little information needed for the characterization of drug release form sustained release matrix tablets. For more thorough information regarding the change of release mechanism and mean dissolution time (MDT), due to incorporation and gradual increase of the amount of SLS, the dissolution data obtained were treated with well known Korsmeyer's equation which is also known as exponential equation. Value of release exponent (n) of formulation-1 obtained form Korsmeyer's equation was 0.847, indicated that in the absence of SLS the drug release mechanism was almost controlled by polymeric erosion and swelling. The straight line (Figure 1) obtained in this case also indicated that the drug release rate didn't not change over time and zero-order release mechanism is the dominant mechanism in this case. Release exponent values of formulation-2 to formulation-7 showed an interesting trend of release mechanism. As the amount of SLS increased the release patterns gradually shifted to diffusion controlled mechanism from erosion and swelling dominated mechanism. Formulations containing 5 mg (n=0.702) and 10 mg (n=607) SLS followed anomalous release mechanisms also termed as first order release. In these cases no mechanism of drug release was dominated over other mechanism(s); for example, polymer erosion, swelling, polymeric chain relaxation, solvent penetration, hydrophilic gel formation and diffusion were contributing in almost comparable extents. Relatively lower n values of formulation-4 and formulation-5 suggested that, the release mechanism showed a clear shift towards Fickian diffusion mechanism, though some non-Fickian contributors of release mechanism were playing insignificant role. The n values of last two formulations were 0.375 and 0.424, respectively where SLS content was the highest, the release mechanisms were clearly dominated by Fickian diffusion which was also supporting the trend found in this study. That happened possibly due to the solubility enhancement of carbamazepine, which was attributed to gradual increase of SLS content in tablet matrices.

From the dissolution data (Table 2) and figure 2, it was clear that values of mean dissolution time (MDT) gradually reduced as well as the release rate was increased because of increased SLS content of tablet formulations. For example, MDT value of formulation-1 was 14.3 hrs whereas that for formulation-7 was 6.9 hrs. This reduction in the magnitude of MDT is the most valuable observation which indicates that when the amount of SLS was increased, the drug release rate was increased gradually. Such increase of drug release rate and extent due to increase SLS content was possibly due to the formation of channels which stimulated the penetration of water into the inner part of the matrix causing the exposure of new surfaces of tablet matrix to the dissolution medium. Another reason may be due to enhanced erosion of polymer which results in faster diffusion of drug from the matrix of polymer into the dissolution media. Similar observations were seen by Sung and coworkers (Sung *et al.*, 1996) while they were evaluating the effect of formulation variables on drug and polymer release from HPMC-based matrix tablets.

Conclusion

From the above observations an important conclusion can be drawn that an increase of SLS content increases the of rate and extent of carbamazepine release. In all these cases, the increase of the amount of SLS gradually enhanced the release of drug in dissolution study which is supported by the values of MDT. Thus, a suitable combination of Methocel K15MCR and SLS can give us matrix system with desirable drug release.

Table 1. Formulations of carbamazepine matrix tablets containing different amounts of sodium lauryl sulfate (SLS).

Ingredients (mg)	Formulations						
	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Carbamazepine	200	200	200	200	200	200	200
Sodium Lauryl Sulfate (SLS)	0	5	10	15	20	25	30
Avicel PH101	80	80	80	80	80	80	80
Methocel K15MCR	200	200	200	200	200	200	200
Magnesium Stearate	4	4	4	4	4	4	4
Total wt/Tab	484	489	494	499	504	509	514

Table 2. Different release parameters of Methocel K15MCR based matrix tablets of carbamazepine.

Formulation	% Release after 8 hour	Zero Order		Higuchi		Korsmeyer		MDT (Hour)
		k_o	R^2	k_H	R^2	n	R^2	
F-1	33.7±1.25	4.12	0.991	12.4	0.969	0.847	0.998	14.3±0.78
F-2	35.2±1.62	4.14	0.975	12.5	0.967	0.702	0.982	12.9±0.60
F-3	38.8±1.78	4.51	0.954	13.9	0.984	0.607	0.985	12.2±0.57
F-4	42.5±1.85	4.83	0.889	15.5	0.992	0.520	0.983	11.5±0.68
F-5	48.9±1.56	5.60	0.890	17.9	0.984	0.577	0.967	8.7±1.12
F-6	52.4±1.75	5.42	0.882	18.1	0.977	0.375	0.989	6.9±1.01
F-7	55.1±2.32	6.04	0.902	19.3	0.994	0.424	0.981	6.8±0.96

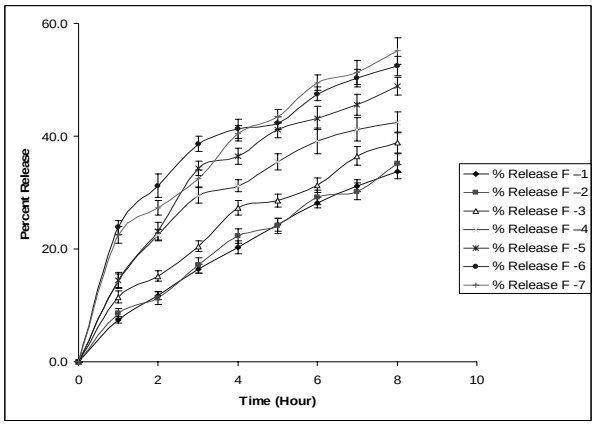

Figure 1. Zero order release pattern of Methocel K15MCR based matrix tablets of carbamazepine containing different amount of SLS.

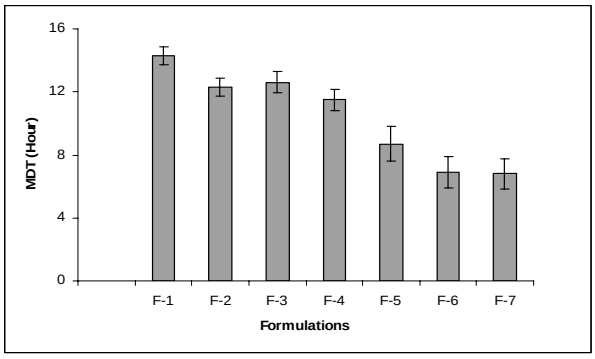

Figure 2. Mean Dissolution Time (MDT) of different formulations containing different amounts of SLS.

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