Study and Evaluation of Release Kinetics of Tramadol HCl from Lipid Based Sustained Release Capsules by Melt Matrix

Irin Dewan, Ananta Saha, S.M. Ashraful Islam, Mahjabeen Gazi, Tasnuva Amin and Sayeeda Fahmee Chowdhury

Department of Pharmacy, University of Asia Pacific, Dhanmondi, Dhaka-1209, Bangladesh

ABSTRACT: The aim of our study was to improve the dissolution of Tramadol hydrochloride (TH) *via* its semisolid filled lipid based capsules. Sustained release formulation is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Semisolid matrixes of TH were prepared by melt-matrix method and were filled in hard gelatin capsule shell (size 0). In this experiment, a mixture of Glycerol monostearate (GMS) and lipid materials like different lipophilic oils and surfactants were used to improve the matrix integrity and drug release. The effects of different oils like Arachis oil, Soyabean oil, castor oil, neobee oil and olive oil and different surfactants such as Span 80, Tween 80, PEG 400, Chremophore RH 40, Cremophor EL were analyzed by formulating at various ratios. The matrices were subjected to the paddle dissolution method using 900 ml of phosphate buffer (pH 6.8). The dissolution test was performed at 100 RPM and the temperature was set at 37 ± 0.5 ^{0}C. The amount of drug was measured from the absorbance with a UV spectrophotometer at 270 nm. The release of drug was plotted in zero order-, 1st order- and Higuchi-release patterns. The correlation coefficients values of the trend lines of the graphs revealed that the formulations best fit in Higuchian release pattern. So it can be said that the pharmaceutical quality of Tramadol HCl capsules can be improved by using a semisolid lipophilic matrix filled in hard gelatin capsules.

Key words: Melt matrix, Tramadol hydrochloride, hard gelatin capsule shell, dissolution, lipid materials.

INTRODUCTION

Tramadol, a synthetic opioid of the aminocyclohexanol group, is a centrally acting analgesic with weak opioid agonist properties shown in figure 1. Tramadol has been proved to be effective in both experimental and clinical pain without causing serious cardiovascular or respiratory side effects. The half-life of the drug is about 5.5 hours and the usual oral dosage regime is 50 to 100 mg every 4 to 6 hours 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 desirable. The drug is freely soluble in water and hence judicious selection of release retarding excipient is necessary to achieve a constant *in vitro* release.[1]

Correspondence to: Irin Dewan
E-mail: irin_d@yahoo.com

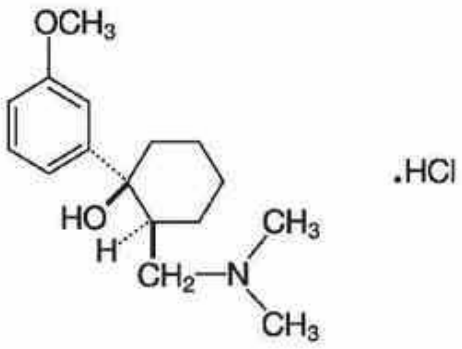

Figure 1. Stucture of Tramadol hydrochloride

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.[2] 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.[3]

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. [4]

Interest in liquid and semisolid matrix (SSM) filling of hard gelatin capsules was renewed in the late 1970s.[5] 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.

The drug release for extended duration, particularly for highly water-soluble drug, using a hydrophilic matrix system is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs with high water solubility, hydrophobic polymers (waxes) are suitable as matrixing agents for developing sustained-release dosage forms. Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications.

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.[6-8]

Tramadol hydrochloride was the model drug in this study which was incorporated in lipid-based semisolid matrix systems to extend its release. In this experiment, different lipophilic oils like Arachis oil, Soyabean oil, castor oil, neobee oil and olive oil and different surfactants such as Span 80, Tween 80, PEG 400, Chremophore RH 40, Cremophor EL were used as the matrix former.[9]

In the present study, various matrix systems were designed and tested for controlled delivery of tramadol. The objectives of the study were to investigate the performance of hydrophobic matrix system in controlling the release of this freely soluble drug, and to investigate the effect of lipid matrix as a release-retarding agent, either in the solid melt matrix, so called a hot melt technology when the lipid matrix is being melted with incorporating the drug and defined the release rate of tramadol.[10,11]

MATERIALS AND METHODS

Tramadol Hydrochloride was a generous gift from Zydus Cedila (Cedila Healthcare LTD, INDIA). Glyceryl monostearate (GMS), Cognis, Germany; PEG 400, Loba Chemie, India; Soyabean oil, Kuok oils & Grains Pvt. Ltd. Singapore; Tween 80, ICI Limited, India; Span 80, BDH Chemicals Limited, England; Span 60, BDH Chemicals Limited, England; Span 20, BDH Chemicals Limited, England; Arachis oil, BDH Chemicals Limited, England; Castor oil, BDH Chemicals Limited, England; Olive oil, Lucy Oliva, Spain, Cremophore RH 40, BASF, Germany; Cremophore EL, BASF, Germany; Solutol HS , BASF, Germany; Di-sodium hydrogen phosphate, Loba Chemie, India; Potassium di-hydrogen phosphate, Loba Chemie, India were received from their respective sources.

METHODS

Preparation of semisolid melt-matrix of tramadol HCl. The semisolid lipid matrix was prepared by melt matrix method. According to tables 1-3, the model drug and lipidic excipients accurately weighted and were placed in a 15-ml glass vial and heated on a hot magnetic stirrer to melt the ingredients at the temperature of 70-80ºC. In each case, the mixture was withdrawn by a glass syringe at the volume of 0.5ml for each time and the semisolid matrix was filled in the size 0 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 shown in Figure 2. After solidification of the melt matrix, the capsule shells were stored in an air tight container.

***In vitro* dissolution study of solid melt matrix.** *In vitro* dissolution studies from the formulations were carried out for 8, 12 and 24 hours in phosphate buffer (pH 6.8). The solid melt matrices were subjected to the paddle dissolution method using 900 ml of phosphate buffer. The dissolution test was

performed at 100 RPM and the temperature was set at 37 ± 0.5ºC. At different interval, samples of 5 ml were withdrawn, filtered and assayed by online spectrophotometer (UVmini-1240, Shimadzu Corporation, Japan) at 270 nm. After each sampling, equal volume (5 ml) of fresh phosphate buffer with the same temperature was replaced.

Analysis by Fourier Transform Infrared (FTIR) spectroscopy. The pure drug and different formulations were subjected to IR spectroscopy using FT-IR spectrophotometer 8400S (SHIMADZU, Kyoto, Japan) shown in figure 8. Their spectra were obtained over the wave number range of 4000 - 400 cm^{-1}.

Table1. Formulations for GMS based melt matrix with different lipophilic oils.

Ingredients	F1	F2	F3	F4	F5
Tramadol Hydrochloride (g)	0.5	0.5	0.5	0.5	0.5
Glyceryl Monostearate (g)	1	1	1	1	1
Soyabean Oil (g)	1.5				
Arachis Oil (g)		1.5			
Castor Oil (g)			1.5		
Olive Oil (g)				1.5	
Neobees oil (g)					1.5

Table 2. Formulations for GMS based melt matrix with different surfactants.

Ingredients (g)	F1	F2	F3	F4	F5	F6	F7	F8
Tramadol Hydrochloride	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
GMS	2	2	2	2	2	2	2	2
Span 80	0.5							
Span 60		0.5						
Span 20			0.5					
Macrogel-20-Stearate				0.5				
Solutol-HS					0.5			
Cremophore RH-40						0.5		
Cremophore EL							0.5	
Tween 80								0.5

Table 3. Formulations for GMS based melt matrix with different concentration of surfactants along with Soyabean oil.

Ingredients (g)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Tramadol	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
GMS	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Soyabean oil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Tween 80	0	0.025	0.05												
Cremophore EL				0	0.025	0.05									
Cremophore RH-40							0	0.025	0.05						
Span 80										0	0.025	0.05			
PEG 400													0	0.025	0.05

Study of differential scanning calorimetry (DSC) thermograms. The differential scanning calorimetry (DSC) thermograms were recorded for tramadol using a differential scanning calorimeter (Perkin-Elmer) in figure 9. Approximately 2-5 mg of each sample was heated in an open aluminum pan from 0-400°C at a scanning rate of 10°C/min under stream of nitrogen.

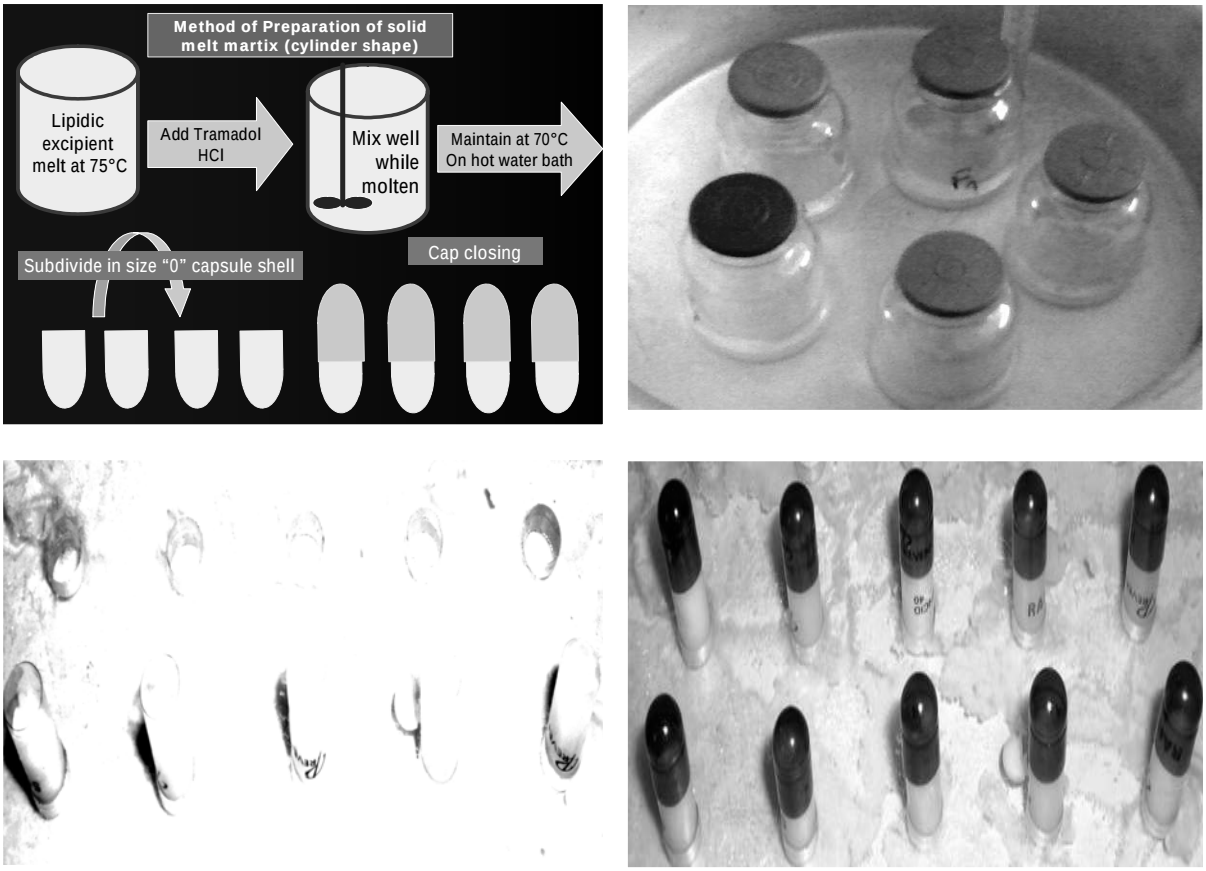

Figure 2. Schematic diagram of the preparation of solid lipid melt matrix in the capsule shell (size 0).

RESULT AND DISCUSSION

Tramadol Hydrochloride is a potent centrally acting analgesic and is used for the management of moderate to moderately severe pain in adults. It is highly water-soluble drug and the present study was aimed to observe release pattern of drug from the melt matrix by using different lipidic excipients, such as Glyceryl monosterate (GMS), Polyethylene glycol 6000 (PEG 6000), Polyethylene glycol 400 (PEG 400), Soyabean oil. The efficacy of these lipidic excipients on drug release was also evaluated with Span 80, Tween 80, Cremophor EL, Cremophor RH 40 in terms of *in vitro* drug dissolution. The variables affecting drug dissolution was matrix property, lipid excipients loading and physicochemical property of the drug molecule. Secondary curve was obtained from the release rate of the different formulations.

Effect of different oils on the release of Tramadol HCl from GMS based melt matrix. Figure 3 shows the release of Tramadol HCl from GMS-Oil melt matrix. 1.5gm of Soyabean oil (F1), Arachis oil (F2), Castor oil (F3), Olive oil (F4), and Neobee oil (F5) was added with same amount of GMS and Tramadol HCl to observe the effect of various oils on the release of Tramadol HCl. It was observed that at 8 hours of *in vitro* dissolution study, F1 (Soyabean oil) gave 29% release, F2 (Arachis oil) gave 33% release, F3 (Castor oil) gave 32% release, F4 (Olive oil) gave 28% release and F5 (Neobee oil) gave 32% release of drug. The release rate was very slow because these oils are hydrophobic in nature and used as the release retarding agent according to figure 4. This test was performed to choose the oil for

further use in some other formulations. It was observed that the release pattern from soyabean oil was quite better in comparison to other oils. From the table 4 it was observed that all formulations followed Higuchi release kinetics.[12]

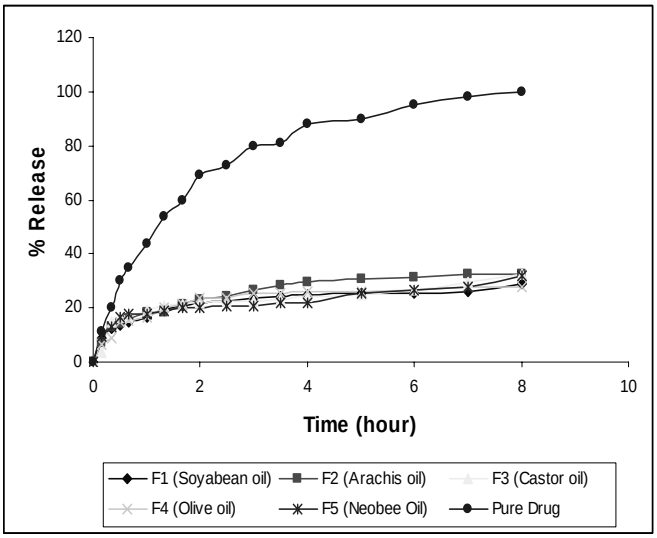

Figure 3. Percent (%) release of different oils from Tramadol HCl containing GMS melt matrix.

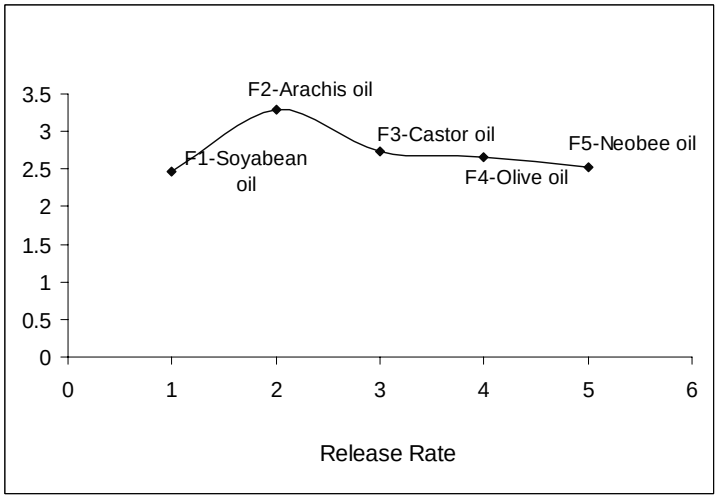

Figure 4. Release rate of different oils formulations from Tramadol HCl containing GMS melt matrix.

Table 4. R^2 value for release kinetics of Tramadol HCl containing GMS melt matrix.

GMS- Oil - Tramadol HCl melt matrix	R^2 value		
Formulation	Zero order	First order	Higuchi square root
F1	0.6662	0.7056	0.9011
F2	0.7586	0.8030	0.9371
F3	0.6729	0.7271	0.9463
F4	0.6099	0.6412	0.9333
F5	0.7297	0.7805	0.9275

Effect of various surfactants on the release of Tramadol Hydrochloride from GMS-surfactant melt matrix. Figure 5 shows the release profile of Tramadol Hydrochloride from GMS-surfactants melt matrix. 1.5 mg of Span 80, Span 60, Span 20, Macrogel-20-stearate, Solutol HS, Cremophor RH 40, Cremophor EL and Tween 80 was added with constant amount of GMS and Tramadol HCl for the formulation of F1, F2, F3, F4, F5, F6, F7 and F8 respectively. *In vitro* dissolution study for 8 hours showed that release rate was different for various surfactants. 63%, 77% and 100% drug was released from Span 80 (F1), Span 60 (F2) & Span 20 (F3) matrices, respectively 57% drug was released from Macrogel-20-stearate (F4), while 92% drug was released from solutol HS (F5). Drug release was 92% and 88% from the formulation F6 (Cremophor RH-40) and formulation F7 (Cremophor EL), respectively. Figure 6 has shown the highest drug release rate for formulation F8 (Tween 80) about 100% in 6 hours. This may be due to the high HLB value of Tween 80. From the table 5 it was observed that all formulations followed Higuchi release kinetics.

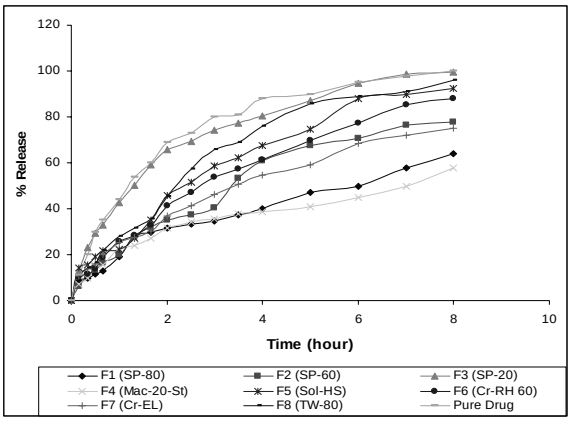

Figure 5. Percent (%) Release of Tramadol Hydrochloride from GMS-Surfactantl melt matrix

Effect of different concentrations of oils on the release of Tramadol Hydrochloride in GMS-Soyabean oil melt matrix. Figure 7 has shown the release of Tramadol Hydrochloride from GMS-Soyabean oil-Tween 80 melt matrix. In all the formulations F1-F3 the amount of lipidic excipients was remain constant but the amount of Tween 80 was gradually increased. *In vitro* dissolution test was performed for 12 hours and it was found that Tween 80 has a marked effect on the release of Tramadol HCl. Formulation F1 (Tween 80-0%) showed 35% drug release after 12 hours. After the addition of Tween 80 the release was 80% and 95% at 12 hours from F2 and F3 respectively. A slight addition of Tween 80 gave a significant release of the drug. The reason behind this may be due to the high HLB value of Tween 80 in the matrix which makes it more soluble.

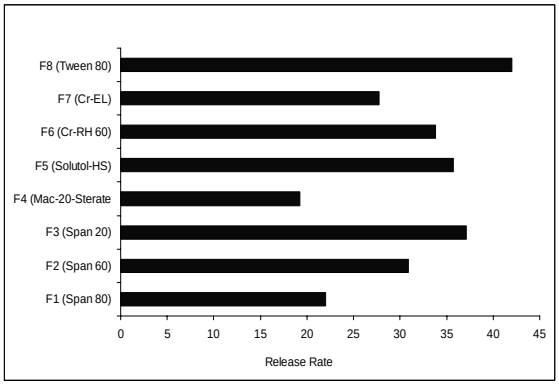

Figure 6. Effect of various surfactants on the release rate of Tramadol HCl from GMS based melt matrix.

Table 5. R^2 value for release kinetics of Tramdol HCl for GMS based melt matrix with different surfactants.

GMS-Surfactants- Tramadol HCl melt matrix Formulation	R^2 value		
	Zero order	First order	Higuchi square root
F1	0.9284	0.9702	0.9834
F2	0.9409	0.9651	0.9988
F3	0.8352	0.9463	0.9836
F4	0.8879	0.9406	0.9833
F5	0.9399	0.9621	0.9992
F6	0.9487	0.9727	0.9900
F7	0.9397	0.9629	0.9981
F8	0.9453	0.9526	0.9979

It was found that Cremophor EL has a marked effect on the release of Tramadol HCl. Formulation F4 (Cremophor EL-0%) showed 35% release of drug after 12 hours. After the addition of Cremophor EL the release of drug was drastically increased.

Formulation F5 (Cremophor EL-5%) showed 98% release of drug after 12 hours and formulation F6 (Cremophor EL-10%) showed 100% release of drug after 12 hours. This high release rate of drug from these matrices may be due to the high solubility of Cremophor EL in the matrices.

From figure 7, it was found that Cremophor RH 40 has a marked effect on the release of Tramadol HCl. Formulation F7(Cremophor RH 40-0%) shows 37% release of drug after 12 hours. After the addition of Cremophor RH 40 the release of drug was drastically increased 82% and 98% from F8 and F9 respectively after 12 hours. This high release rate of drug from these matrices may be due to the high solubility of Cremophor RH 40 in the matrices.[13]

Figure 7 shows the release of Tramadol HCl from GMS-Soyabean oil-Span 80 melt matrix. Formulation F10, F11 and F12 showed 46%, 76% and 80% release of the drug after 12 hours of in vitro dissolution test respectively. The release rate from Span 80 was low which may be due to the low HLB value of Span 80.[14]

Figure 7 demonstrates the release of Tramadol Hydrochloride from GMS-Soyabean oil-PEG 400 melt matrix. *In vitro* dissolution study was performed for 12 hours and it was found that the release was increased with the increased concentration of PEG 400. Formulation F13, F14 and F15 showed 27%, 92% and 95% release of drug after 12 hours, respectively. It was found that PEG 400 has a significant effect on the release of drug and the release rate can be controlled by adjusting the amount of PEG 400. The high release rate of drug from these matrices may be due to the high solubility profile of PEG 400. From the graph it is found that all the formulation F1-F14 follows Higuchi release kinetics.

Drug-polymer compatibility study by Fourier Transform Infrared (FTIR) Spectroscopy. According to figure 8 it was found that IR spectrum of tramadol hydrochloride showed a broad peak at 3305 cm^{-1} may be due to hydrogen bonding, 3046 cm^{-1} may be due to aromatic C-H stretching, 2924 cm^{-1} may be due to C-H stretching of $–OCH_3$, 2510, 2850 cm^{-1} may be due to C-H stretching of $–CH_2$ and - CH_3 groups. 1604, 1570 cm^{-1} may be due to C=C ring stretching. 1280, 1300 cm^{-1} –C-H bending of symmetric and asymmetric of – CH_2 and - CH_3 groups. 1042 cm^{-1} may be due to –C-O-C group. 780 cm^{-1} may be due to substituted benzene ring. From these, it was clear that, there was no appreciable change in the positions of the characteristic bands of the drug along with the IR spectrum of the best formulation derived during the present investigation. Since there is no change in the nature and position of the bands in the formulation, it can be concluded that the drug maintains it's identity without going any chemical interaction with the polymers used.

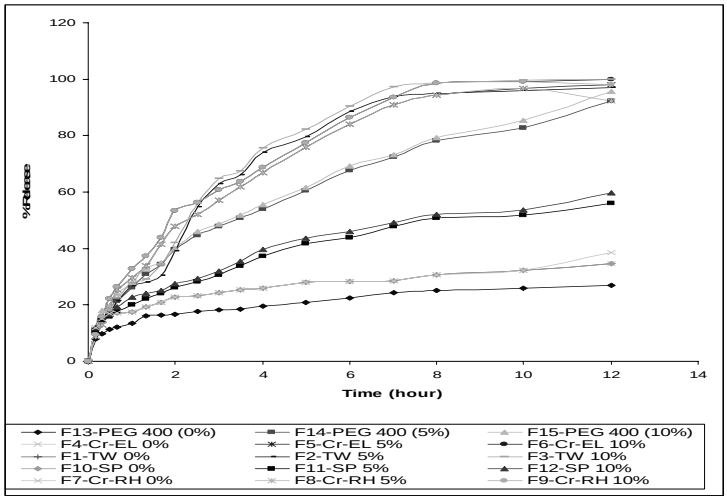

Figure 7. Percent (%) release of different oils with different concentration from Tramadol HCl containing GMS-Soyabean oil melt matrix.

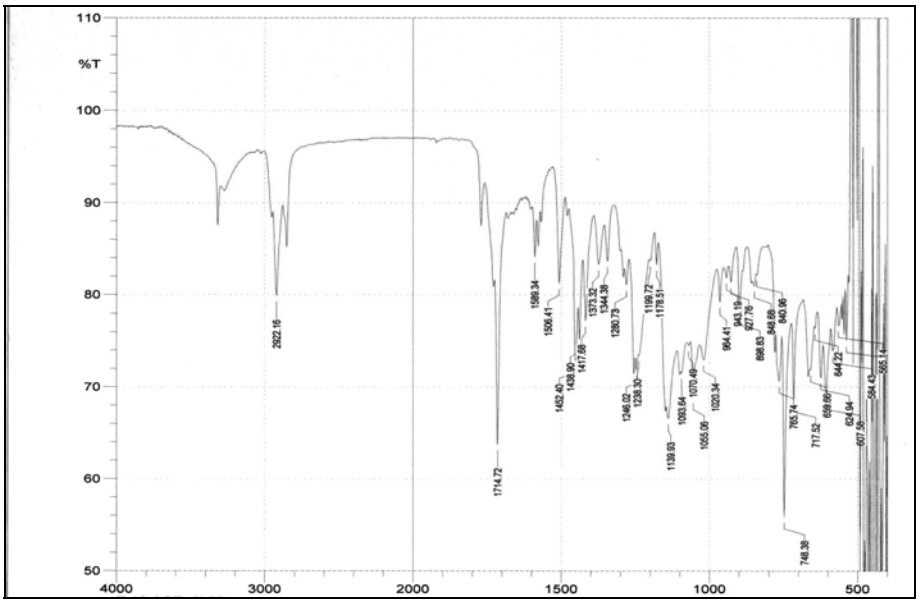

Figure 8. FT-IR spectra of Tramadol hydrochloride containing Arachis oil formulation F2.

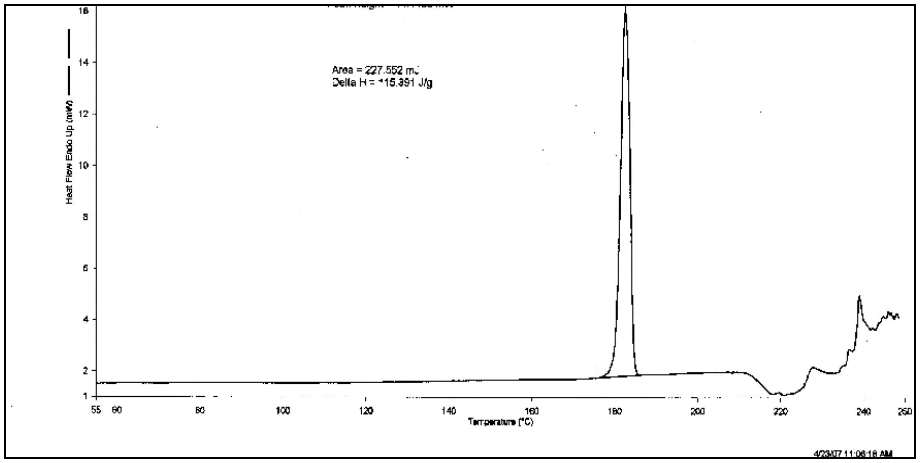

Figure 9. DSC of Tramadol Hydrochloride.

Analysis by differential scanning calorimetry (DSC). Figure 9 shows the DSC thermographs of pure drug Tramadol HCL. Thermographs obtained by DSC studies, revealed that the melting point of pure drug is 185^{o}C. It may be concluded that, the drug is in the same pure state even in the formulation without interacting with the polymers.

CONCLUSION

The level of drug loading had very little effect on dissolution results. The choice of lipid excipients was found to have a much more significant impact. The dissolution profiles observed were consistent with the known behavior of the excipients used. In an attempt to prolong drug release using combination of waxes, it was observed that significant improvement in the release retardant activity was found in the melt matrix containing a higher percentage of waxes. As hydrophilic matrix could not control the Tramadol release effectively for more than 12 hours, it is evident from the results that the hydrophobic matrix prepared by the GMS based lipid excipients provide a better system for controlled delivery of a highly

water soluble drug, like Tramadol Hydrochloride. On the other hand, using solubilizing agent at a very small ratio provided an increasing release effectively from the melt matrix. Further study in this field is still required to establish this controlled release drug delivery system so that in future it can be used effectively in commercial basis.

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