8.1 Tramadol Hydrochloride

Tramadol Hydrochloride is highly soluble in water (BCS class I drug). For sustaining release of drug high viscosity hydrophilic polymers and lipophilic (wax) substances were used. FTIR and DSC study indicated there was no drug polymer, drug excipient incompatibility.

a) Hydrophilic Polymer system

1) As tramadol HCl is highly soluble in water, for sustaining release of drug for 16 hrs, 30% w/w concentration of HPMC K100M was required. Low viscosity grades of HPMC cannot sustain the release of drug. High viscosity grades of HPMC were required. This may be due to swelling capacity and gelling strength of HPMC K100M is more as compared to other polymers. Sustained release effect was found in order of HPMC K100M > Xanthan gum > Polyox WSR 301.

2) Intrgranulation method was found to be better than extragranulation method for sustaining release of drug in all hydrophilic polymer system.

3) Formulation T12 (HPMC K100M 30% and ethyl cellulose 10%) showed more similarity with the dissolution profile of marketed product ($f_2$ - 90.96)

4) Dicalcium phosphate was found to be the best suitable excipient in all hydrophilic matrices which helps in sustaining release of drug may be due to its insoluble nature.

5) No significant effect on release profile of drug was found after addition of ethyl cellulose in hydrophilic polymers.

6) The drug release from hydrophilic polymer matrix system showed peppas and matrix as best fit model. Most of the formulations showed fickian diffusion mechanism for the release of drug.

7) Formulations T8, T12 of intragranulation method and T14, T18 of extragranulation method showed $f_2$ value more than 70. Formulation T12 showed $f_2$ value of 90.39.

b) Wax matrix tablet

1) Formulation containing hydrogenated vegetable oil showed more sustained release effect as compared to other waxy substances. Sustained release effect was found in order of HVO > Compritol > Precirol. This may be due to more lipophilicity imparted
by HVO to system. It was also found that as ratio of drug:wax increases, the release of drug decreases. This may be due to more lipophilicity imparted by more quantity of wax in matrix system.

2) Addition of excipients showed increase in release of drug as compared to wax matrix tablet without excipient. Addition of lactose showed faster release of drug by erosion mechanism. Addition of dicalcium phosphate can retard release of drug as compared to microcrystalline cellulose and lactose. Presence of lactose in lipophilic matrix (wax matrix) showed increase in release of drug due to soluble nature while MCC gets swelled in matrix which creates channel and increases dissolution.

3) There was no significant effect of sintering time but significant effect of sintering temperature was found.

4) Most of the formulations showed release of drug by matrix diffusion kinetics.

5) Dissolution profile of formulation TM4 showed similarity factor close to marketed product ($f_2$ $≈$ 77.06).

c) Three Layer Tablet System

Formulation TL9 showed similarity factor ($f_2$) of 51.17. Presence of additional hydrophilic polymer over wax matrix tablet showed more sustained effect due to additional barrier for the release of drug. Presence of polymer type, type of excipients in outer coat showed effect on release of drug. Peppas and matrix diffusion was found to be best fit model for release of drug. All the formulations showed nonfickian diffusion mechanism for the release of drug.

d) Tablet in tablet system

Formulation TT10 showed similarity factor ($f_2$) of 82.32 and hence considered to be the best formulation. Presence of polymer type, type of excipients in outer coat showed effect on release of drug.

In both c and d, the release of drug showed peppas and matrix diffusion as best fit model. All the formulations showed nonfickian diffusion mechanism for the release of drug. Tablet in tablet system sustains more release of drug as compared to three layer tablet system.
e) **Stability study:**
No significant effect of storage condition was found on tablet prepared by hydrophilic polymer while slight change in colour and appearance of tablet was found in lipophilic matrix (wax matrix). No significant change was found on cumulative % drug released in both systems.

f) **Optimisation study:**
Optimisation study was carried out using $3^2$ full factorial design. Effect of combination of high viscosity polymers HPMC K100M and polyox WSR301 were studied. For D1, D4 and D12 values of A and B were found to be significant ($P < 0.05$). It indicates both HPMC K100M and polyox WSR301 were having significant effect on release profile of drug. The values of coefficient for individual polymer was found to have negative sign which indicates that as concentration of both polymers was increased it helped to sustain the release of drug. For $T_{25}$, $T_{50}$ and $T_{75}$ the values A and B were found to be significant ($P < 0.05$). The values of coefficient for individual polymer were found to have positive value which indicates that as concentration of polymer was increased time required for release of drug also increased.

**8.2 Metoprolol Succinate**
Metoprolol succinate is highly soluble drug (BCS class I). Preformulation study was carried out. FTIR and DSC study showed that selected polymers, wax and excipients were compatible with drug.

a) **Using hydrophilic polymer**

It was observed that carbopol 971P, HPMC K100M and xanthan gum (30%) sustained release of drug upto 20 hrs. These polymers showed sustained release effect upto 20 hrs may be due to high swelling capacity when come in contact with dissolution media. Carbopol 971P can retard initial release of drug also due to its fast swelling capacity. Hence carbopol 971P was found to be most suitable polymer for this system. Gelling strength and firmness of gel was found to be more with carbopol 971P. Polyox WSR 301 (30 %) sustained release of drug upto 16 hrs. In case of xanthan gum it was observed that polymer get swelled in dissolution media...
but after sometime showed erosion also. In case of Polyox WSR 301 polymer get swelled fast but also gets eroded fast. Faster release was found from polyox matrix. The rate of erosion was found to be more for Polyox WSR 301 than xanthan gum. The sustain action of polymer was found in following order
Carbopol 971 P > HPMC K100M > Xanthan gum > Polyox WSR 301

2) In case of HPMC K100M, matrix tablet was prepared using 20, 30 and 40% concentration. Concentration of 20% sustained release of drug upto 16 hrs only and initial release of drug was also found to be fast. While concentration of 30 and 40% sustained the release of drug upto 20 hrs. Low concentration of polymer may not be sufficient to form viscous gel around tablet to control release of drug. Hence as time passes intactness of matrix was found to decrease and matrix showed erosion and release of drug was found fast. At concentration of 30 and 40% polymer get swelled to its full extent and formed viscous gel around tablet and lasts till the end of dissolution. Due to formation of swollen matrix diffusional barrier increased which sustained release of drug. Initial release of drug was found to be fast due to slow swelling of high viscosity polymer but once swelled it sustains the release of drug till the end. No significant effect was found on release profile of drug when concentration of HPMC K100M was changed from 30 to 40%. Hence 30 % concentration may be sufficient to sustain the release of drug upto 20 hrs.

3) Carbpol 971P (30 and 40%) showed sustained release effect for 20 hrs. This may due to swelling and gelling capacity of polymer is more. Concentration of 30 % is sufficient to sustained the release of drug for 20 hrs.

4) In case of 20% xanthan gum, release of drug was found to be upto 16 hrs and with 30% it was found to be upto 20 hrs. When polyox WSR 301 was used, it was found that 30 % concentration of polymer sustained release of drug upto 16 hrs while 40% concentration showed sustained effect upto 20 hrs.

5) It was observed that when Carbopol 971P (40%) was used alone sustained release of drug upto 20 hrs (T<sub>90</sub> > 20 hrs). This may be due to rapid uptake of water which causes fast swelling of polymer and gelling capacity and gelling strength of polymer is good. While in case of Polyox WSR 301 (40%) T<sub>90</sub> value was found to be 15 hrs. When combination of polymer carbopol 971P (20%) and Polyox WSR
301 (20%) was used. \( T_{90} \) was found to be 16 hrs. The decrease in time for dissolution may be due to presence of polyox in carbopol matrix system. The presence of polyox causes erosion of matrix and faster release of drug occurred as compared to carbopol matrix alone.

6) In dissolution study of formulation containing HPMC K100M alone, it was found that initial release of drug was faster. When carbopol 971P was mixed with HPMC K100M, it sustained initial release of drug. It was observed that if concentration of Carbopol 971P in matrix was more, it sustained release of drug for time.

Combining HPMC K100M with Carbopol 971P in a matrix resulted in slower drug release. This has been related to a synergistic increase in the viscosity and therefore gel strength of the matrix, possibly due to stronger hydrogen bonding between –OH groups of HPMC and carboxylic groups of Carbopol 971P. This stronger hydrogen bonding between the polymers resulted in a more rigid structure through which drug diffusion can occur.

7) No significant change in release profile of drug from HPMC K100M matrix system containing dicalcium phosphate (DCP) and Microcrystalline cellulose (MCC). Due to insoluble nature of DCP, it retards release of drug. While in system containing MCC, slightly faster release of drug was observed. MCC is having property of slightly swelling in hydrophilic matrix system which forms channels for entry of dissolution media and causes release of drug.

8) Formulation M11 showed maximum \( f_2 \) value of 76.52 and hence was selected for further stability study.

9) Marketed product showed Peppas as best fit model and release of drug by nonfickian diffusion mechanism. Most of the formulations of hydrophilic polymer matrix showed matrix diffusion as best fit model while release was found either by fickian or nonfickian diffusion mechanism.

**b) Wax matrix tablet**

1) The sustained release effect was found to be more with hydrogenated vegetable oil. This may be due to more lipophilicity of HVO. The release retardant effect was found in order of HVO > Compritol > Precirol
2) As ratio of drug:wax was increased, it was found that the release retardant effect also increased. This may be due to more lipophilicity imparted by system.

3) When wax matrix tablet was prepared by combination of two waxes, it showed more retardant effect on release of drug than wax substance alone. This may be due to synergistic effect which imparts more lipophilicity to matrix tablet than any wax alone.

4) Wax matrix tablets having dicalcium phosphate retarded release of drug for more time may be due to insoluble nature of dicalcium phosphate. Wax matrix tablet containing lactose showed release of drug fast may be due to dissolution of lactose and formation of aqueous channels and pores in matrix. Tablet containing microcrystalline cellulose showed release somewhat faster that DCP containing matrix may be due to slight swelling capacity of MCC which causes channel formation and cracks in matrix to increase dissolution of drug.

Wax matrix tablets alone without any excipients were found to retard release of drug for more time than tablet without any excipient. This may be due to excipients which disturbs intactness of matrix.

5) No significant effect of sintering time but significant effect of sintering temperature was found.

6) Formulation MM9 showed maximum $f_2$ value of 65.33 and hence was selected for stability study.

7) In case of wax matrix tablet, most of the formulations showed Peppas as best fit model. All the formulations showed release by nonfickian diffusion mechanism.

c) Stability study:

i) Tablets prepared from hydrophilic polymer system not showed significant effect of storage condition on stability of product. No significant change was observed in % dug content, hardness and cumulative % drug release. Slight change in appearance and colour of tablet was observed. Overall tablet was found to be stable.

ii) In stability study of wax matrix tablet, somewhat increase in dissolution of drug was observed but that was not significant. Tablet became somewhat rough. No change in hardness, % drug content was observed.
d) Optimisation Study:
Optimisation study was carried out using $3^2$ full factorial design. Effect of combination of high viscosity polymers HPMC K100M and carbopol 971P were studied. For D1, D4 and D12 values of A and B were also found to be significant ($P < 0.05$). It indicates both HPMC K100M and Carbopol 971P were having significant effect on release profile of drug. The values of coefficient for individual polymer was found to have negative sign which indicates that as concentration of both polymers was increased it helped to sustain the release of drug. For $T_{25}$, $T_{50}$ and $T_{75}$ the values A and B were found to be significant ($P < 0.05$). The values of coefficient for individual polymer were found to have positive value which indicates that as concentration of polymer was increased time required for release of drug also increased.

8.3 Cyclobenzaprine Hydrochloride
Cyclobenzaprine Hydrochloride is highly water soluble drug (BCS class I) having skeletal muscle relaxant effect. FTIR and DSC study indicated that selected polymers, wax and excipients are compatible with drug.

a) Using hydrophilic polymer system
1) HPMC K100M showed more sustained release effect than xanthan gum. But for both polymers concentration of 30% w/w was sufficient to extend the release of drug upto 16 hrs. It was found that as concentration of HPMC K100M increased from 20 to 40 %, the release retardation effect also increased. At low concentration (20%), the release of drug was found within 12 hrs. While in case of 30% and 40% concentration of polymer, release was sustained up to 16 hrs. It was also observed that as concentration of polymer was increased above 30 % no significant change in release profile was observed. This may be due to sufficient swelling of polymer and formation of viscous gel at 30% w/w concentration.

2) Combination of HPMC K100M and xanthan gum in matrix system showed more sustained release effect as compared to these polymers alone. This may be due to rapid hydration of xanthan gum combined with firm gel strength of HPMC K100M. This attributes to slower drug release of highly water soluble drug (Cyclobenzaprine HCl). The initial burst release of highly water soluble drug was controlled by rapid hydration
of xanthan gum whereas subsequent drug release and matrix integrity by firm gel strength of HPMC K100M.

3) Presence of dicalcium phosphate extends release of drug for more time than microcrystalline cellulose in hydrophilic polymer matrix. This may be due to insoluble nature of DCP.

4) Formulation C4 having 30% HPMC K100M and microcrystalline cellulose as an excipient showed more similarity with marketed product in terms of cumulative % drug released \((f_2-79.40\%)\).

5) Marketed product showed release of drug by Peppas kinetics and by fickian diffusion mechanism.

6) The drug release from hydrophilic polymer system showed matrix diffusion kinetics and nonfickian diffusion mechanism.

b) Wax Matrix Tablet

1) It was found that wax matrix tablet prepared using hydrogenated vegetable oil sustained more release of drug as compared to compritol. This may be due to more lipophilicity of HVO.

2) The cumulative % drug release was found to decrease with increase in wax content. This may be due to more lipophilicity imparted by system due to presence of more wax substances.

3) Sustained release wax matrix tablets prepared with lactose showed faster release. This may be due to formation of pores or channels due to dissolution of lactose. Along with dissolution of lactose tablet also eroded and hence release of drug was found to be faster. Wax matrix tablets containing microcrystalline cellulose (MCC) as an excipient showed somewhat faster release as compared to DCP as an excipient. This may be due to slight swelling property of MCC which causes crack formation and creates channel for entry of dissolution medium and causes dissolution of drug. DCP can retard release of drug due to its insoluble tendency. The release of drug from wax matrix tablet showed more sustained release than wax matrix tablet containing excipient. In wax matrix system, drug is uniformly and molecularly dispersed in wax system. When
the granules are compressed, drug remains in contact with wax. Presence of excipients in wax matrix system disturbs the integrity of tablet.

4) The physical mixture of drug and wax substances kept at 80°C for an hour can sustained release of drug for more period of time. There was no significant effect of sintering time but significant effect of sintering temperature was found.

5) The drug release from wax matrix system followed either matrix or peppas kinetics. Formulations showed release of drug either by fickian or nonfickian diffusion mechanism.

6) Formulations CM4, CM7 and CM12 were considered to be the best formulations as f2 value were found to be more.

c) Stability study:
Stability data for hydrophilic polymer system showed no significant change in hardness, % drug content, appearance of tablet and cumulative % drug released.

Stability data of wax matrix system showed slight change in colour and appearance of tablet. No significant change was observed on hardness, % drug content. Slight increase in release of drug was found but that was not significant.

d) Optimisation study:
Study was carried out using 3² full factorial design. Effect of combination of high viscosity polymers HPMC K100M (A) and xanthan gum(B) were studied. Values of A and B were also found to be significant (P < 0.05). It indicates both HPMC K100M and xanthan gum were having significant effect on release profile of drug. For D1, D4 and D12 values of coefficient for individual polymer was found to have negative sign which indicates that as concentration of both polymers was increased it helped to sustain the release of drug. For T₂₅, T₅₀ and T₇₅ the values A and B were found to be significant (P < 0.05). The values of coefficient for individual polymer were found to have positive value which indicates that as concentration of polymer was increased time required for release of drug also increased.
8.4 Aceclofenac:

Aceclofenac is BCS class II drug (insoluble in water). FTIR and DSC study revealed that there was no significant interaction between drug, polymers, wax and excipients.

a) Using hydrophilic polymer

1) Effect of polymer type on release profile of drug:

From dissolution study, it was observed that matrix tablet of HPMC K100LVCR showed faster release of drug than from matrix tablet of HPMC K4M. This may be due to property of HPMC K100LVCR of forming weak gel structure due to limited swelling capacity as polymer is having less viscosity. Mostly polymer undergoes erosion and gets solubilised causing faster release of drug. HPMC K4M is having swelling capacity and hence it sustained release of drug for more time.

2) Effect of polymer concentration on release of drug:

Effect of HPMC K4M concentration was studied. It was observed that when HPMC K4M was used in 10 % concentration sustained the release of drug upto 12 hrs only. While polymer concentration of 12.5% and 15% sustained the release of drug upto 24 hrs. The polymer concentration of 12.5% and 15% was found to be sufficient for giving desired release profile.

3) Effect of release liner on release profile of drug:

At conc. above 15% or above, desired release was not found during initial phase of dissolution. Hence water soluble fillers like lactose and pearlitol were used as release liners. The presence of soluble fillers in matrix system gets solubilised in dissolution media and forms channels for the entry of dissolution media, which causes dissolution and easy diffusion of drug. When release liners were used at low concentration of polymers, it caused erosion of tablet and dissolution was found to be faster. If concentration of release liner were increased it caused faster release of drug. No significant difference was found between lactose and pearlitol as release liner.
4) **Effect of type and concentration of poloxamer on release profile of drug:**

Poloxamer 188 and poloxamer 407 were tried in hydrophilic matrix system to adjust initial and end release profile of drug. It was found that both poloxamers were useful for increasing initial and to adjust end release of drug. It was found that Poloxamer 188 showed faster release from hydrophilic matrix than poloxamer 407 at the same concentration, may be due to more HLB value of Poloxamer 188. Poloxamers get solubilised in dissolution media and form aqueous channels through which dissolution media enters and causes dissolution of drug. Due to surfactant activity of poloxamer, drug may get solubilised in matrix and facilitates diffusion of drug. At higher concentration of poloxamer, matrix integrity of tablet not remains and erosion of tablet was found due to which faster dissolution of drug occurred. Both type of poloxamers in HPMC K100LVCR showed increase in rate of erosion and increased release of drug.

5) Marketed product showed Peppas as best fit model and release of drug was found to be by fickian diffusion kinetics.

6) Most of the formulations of hydrophilic polymer system containing release liner showed Peppas or matrix diffusion as best fit model and release was found to be by nonfickian diffusion mechanism. Formulations containing more quantity of release liner showed release by first order kinetics. Formulation A8 showed maximum $f_2$ value of 55.82 which was selected for stability study.

**b) Wax Matrix System**

As drug was from BCS class II, use of lipophilic substance alone will not give proper release of drug (retardation effect will be more). Hence formulations were prepared containing poloxamer 188 and poloxamer 407.

**Effect of poloxamer type and concentration on release profile of drug from wax matrix system**

Lipophilic matrix containing poloxamer 407 showed faster release as compared to system containing poloxamer 188. This may be due to its swelling properties in presence of water. When matrix system containing poloxamer 407 comes in contact with dissolution media, it may starts swelling and hence produces channels in the matrix system, through which
release of drug occurred fast. As concentration of both poloxamer was increased release was found to be fast. At high concentration it causes faster erosion of wax matrix. Formulation AM3 showed $f_2$ value of 46.67 and selected for stability study.

c) Bilayer tablet technology
Conventional controlled release dosage forms delays the release of drug and do not attain therapeutic concentration of drug. Hence bilayer tablets were preferred. In this, IR layer gets dissolved and adjust therapeutic concentration of drug and SR part maintains therapeutic concentration of drug in body.
All the formulations of bilayer tablet system showed $f_2$ value above 50 and majority of formulations showed $f_2$ value more than 70. Formulation AB7 showed $f_2$ value of 84.93 and was selected for stability study.

d) Tablet in tablet technology
It was consisted of SR part as core tablet which was surrounded by IR part. During dissolution IR part get dissolved and was useful in adjusting initial release profile of drug while SR part maintains further release of drug. For all formulations $f_2$ was found to be more than 65. Formulation AT3 ($f_2$ - 69.89) was selected for stability study.
The release profile of drug from bilayer system and tablet in tablet system showed very similar dissolution profile to marketed product.

e) Stability study
Tablets prepared from hydrophilic polymers not showed significant effect of storage condition on stability of product. Slight change in colour of tablet was observed. It became pale yellow in colour. No significant change was observed in % drug content, hardness and cumulative % drug release. Thus prepared tablets were found to be stable. The tablet prepared by bilayer tablet technology and tablet in tablet also was found to be stable during study. Slight change in colour and appearance of tablet was found. Also no significant change in % drug content, hardness and cumulative % drug release was observed.
In case of wax matrix tablet using poloxamer 407, it was observed that slight increase in release of drug after one month. After that no significant change in release of drug was observed with time. The tablet became soft and surface appeared rough. Darkening in
colour of tablet was found. Hardness of tablet was found to decrease due to softening of tablet.

e) Optimisation study:

i) Effect of lactose on release profile of drug from hydrophilic matrix system

As drug was practically insoluble in water, it was decided to use lactose as release liner in HPMC K4M sustained release matrix system to increase initial release of drug. Lactose was used to form pores and channels through which dissolution media enters and causes release of drug. Optimisation study was carried out by $3^2$ full factorial design. HPMC K4M (A) and lactose (B) was considered as variables. Values of A and B were also found to be significant ($P < 0.05$). It indicates both HPMC K100M and xanthan gum were having significant effect on release profile of drug. Coefficient of A showed negative sign which indicates as concentration of HPMC K4M was increased; it sustained the release of drug. Positive sign for B indicated that as concentration of lactose was increased it increases the release of drug. For $T_{25}$, $T_{50}$ and $T_{75}$ the values A and B were found to be significant ($P < 0.05$). The coefficient of A was having positive sign which indicates that as concentration of HPMC K4M was increased, the time required for release increases. The coefficient of B is having negative sign which indicates that as concentration of lactose was increased, the time required for release decreases.

ii) Effect of poloxamer 407 in lipophilic matrix system

As drug was practically insoluble, poloxamer 407 was included in wax matrix tablet as release liner. At higher concentration of poloxamer 407, release was found to be fast within 12 hrs, this may be due to formation of more aqueous channels and pores in matrix system which can not maintain the integrity of system and faster erosion of matrix occured. Due to surfactant activity of poloxamer wetting of drug occurs and it helps to increase the release of drug. Release retardant effect was found to be more at higher concentration of hydrogenated vegetable oil (HVO) due to more lipophilicity imparted by matrix system. Optimisation study was carried out by $3^2$ full factorial design. Hydrogenated vegetable oil (A) and Poloxamer 407 (B) was selected as variables. The variables A and B were found to be significant. Coefficient of A showed negative sign which indicates that as concentration
of HVO was increased; it sustained the release of drug. Positive sign of B indicated that as concentration of poloxamer 407 was increased it increases the release of drug. In case of For T₂₅, T₅₀ and T₇₅ the values A and B were found to be significant (P < 0.05). The coefficient of A is having positive sign which indicates that as concentration of HVO was increased, the time required for release increases. The coefficient of B is having negative sign which indicates that as concentration of poloxamer 407 was increased, the time required for release decreases.