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Formulation, Development and Evaluation of Sustained Release Matrix Tablet of Tramadol Hydrocholoride Using Various Hydrophilic Natural Polymers

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Abstract— *The main objective of this research work was formulation, develop and evaluation of sustained release matrix tablets of Tramadol Hydrochloride using various hydrophilic natural polymers like acacia, Xanthan gum and gum of tragacanth as non-toxic, easily available and suitable matrix system. Sustained release tablet of Tramadol Hydrochloride were prepared by direct granulation method using different concentrations of hydrophilic natural polymers. The prepare tablet were evaluated for pre- compression such as Bulk density, Tapped density, the angle of repose, Carr's compression index, Hausner ratio and post-compression parameter's such as weight variation, hardness, thickness, friability, drug content, uniformity of drug and in-vitro dissolution studies. FTIR studies shown there was no interaction between drug and polymer. In-vitro drug release using USP dissolution apparatus. The dissolution study revealed that formulations containing the tragacanth as a polymer showed the drug release up to 12 hours and found to be most promising polymer among three polymers used in the research work.*

Keywords— *Tramadol Hydrochloride, Hydrophilic natural gums like Acacia, Xanthan gum and Gum of Tragacanth, Sustained release, Matrix tablet.*

I. INTRODUCTION

Sustained release dosage form is defined as any drug or dosages form modification that prolong the therapeutic activity of the drug. The primary objectives of sustained release drug delivery are to ensure safety and enhancement of efficacy of drug with improved patient compliance. This delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug plasma above the minimum effective concentration and below the minimum toxic level for extended period of time.

Tramadol is a centrally acting analgesic having the amino cyclo hexanol group which has a strong analgesic action similar to μ- opioid profile (Chander et al. 2010). It is administered when non steroidal anti inflammatory drug fail to mitigate pain. It has been in clinical use in Europe since the late 1970 and has been proved to be effective in pain conditions without causing serious cardiovascular or respiratory side effects (Lehmann 1997). Tramadol has high oral bioavailability but it is extensively metabolized (Raffa et al. 1995). The half- life of the drug is about 5.5 hours and the oral dosage regimen is 50mg to 100mg every 4 to 6 hours with a maximum oral dosage of 400mg/day (Alderman., 1984). The reduce the frequency of administration and improve patient compliance, a conventional sustained release formulation of Tramadol hydrochloride is developed. Various researchers have been trying to optimize the therapeutic profile by formulating sustained release dosage forms of tramadol hydrochloride using hydrophilic matrix system (Mishra et al., 2006), water insoluble matrix system (Chander et al., 2010) and natural gums (Raghavendra et al., 2009). But works on bi-layer sustained release tablet of tramadol hydrochloride has not been reported yet. The target of the present study is to achieve suitable tramadol hydrochloride therapeutic profile by formulating bi-layer tablet consisting of a sustained release layer using natural gums like acacia, xanthan gum and gum of tragacanth.

II. MATERIAL AND METHODS

Tramadol Hydrochloride, Acacia, Xanthan gum, Gum of Tragacanth, Lactose, Magnesium sterate and Aerosil was obtained as laboratory sample from Merck chemical Pvt. Ltd.

2.1. Methods

Pre-formulation studies:

2.1.1. Determination of organoleptic properties

The physical appearance of the drug was observed and compared with the pharmacopoeia specifications.

2.1.2. Determination of melting point

The melting point of Tramadol was determined by the capillary method.

2.1.3. Solubility

Small increments of Tramadol was added to 10 ml of solvent (distilled water, acetone, ethanol, diethyl ether, acetic acid) in a 25 ml stoppered standard flask with vigorous shaking. Visually observed the solution, if the solution was clear and no undissolved particles were observed if it was insoluble again another increment of particular solvent was added and the procedure was continued until undissolved tramadol was found.

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2.1.4. Preparation of standard calibration curve of Tramadol Hydrochloride matrix tablet

Spectrophotometric method based on the measurement of absorbance at 271 nm in 0.1N HCl, pH 1.2 and phosphate buffer pH 6.8 was used for the estimation of Tramadol hydrochloride, 100mg of the drug (Tramadol hydrochloride) was dissolved in 100ml of 0.1N HCl (stock solution 1000µg/ml) from this 10ml of solution was taken and the volume was adjusted to 100ml with 0.1N HCl (100µg/ml). The above solution was subsequent diluted with 0.1N HCl, pH 1.2 and phosphate buffer pH6.8 to obtained the series dilutions containing 10,20,40,60 and 80µg/ml of Tramadol hydrochloride solution. The absorbance of the above dilutions was measured at 271nm using the UV visible spectophotometer (Shimadzu) using 0.1N HCl and phosphate buffer as the blank. Then a graph was plotted by taking concentration on X-axis and absorbance on Y-axis which gives a straight line.

2.1.5. Compatibility studies with FTIR Spectrophotometer

The pure drug vand polymer were prepared and scanned from 4000-400cm^{-1}in FTIR spectrophotometer. The FTIR spectrum of the obtained sample of drug and drug with mixture were compared with the standard functional group frequencies of Tramadol Hydrochloride, Acacia, Xanthan gum, gum of Tragacanth respectively. The compatibility between the drug and polymers were evaluated using FTIR peak matching method. The results obtained are shown in Table No.4,5 and Figure No.3,4.

2.1.6. Preparation of sustained release tablets of Tramadol Hydrochloride matrix tablet

Sustained release tablets were prepared by using direct compression method. First of the batches (F1 to F3) were prepared using Acacia. Second set of the batches (F4 to F6) were prepared using Xanthan gum. Similarly third set of the batches (F7 to F9) were prepared by using combination gum of Tragacanth.

Initially drug (Tramadol hydrochloride) and other additives (polymer and diluents) except magnesium sterate and aerosil were passed through 60 mesh sieve and thoroughly mixed in polybeg for 10 minutes.

The magnesium sterate and aerosil was added and further mixed for 5 minutes. The resulting mixture was fed into die of 10 station tablet machine to produce matrix tablets using round pounches of 10mm diameter.

2.1.7. Formulation of Tramadol Hydrochloride matrix tablet

Table No.1. Formulation Batches for Tramadol Hydrochloride

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug(Tramadol)	50	50	50	50	50	50	50	50	50
Acacia	50	100	150	-	-	-	-	-	-
Xanthan gum	-	-	-	50	100	150	-	-	-
Tragacanth	-	-	-	-	-	-	50	100	150
Lactose	197	147	97	197	147	97	197	147	97
Mg. Sterate	2	2	2	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1	1	1	1
Total weight	300	300	300	300	300	300	300	300	300

2.1.8. Evaluation of Pre-compression parameters of powder blend

The prepared powder mixtures were evaluated for the blend property like bulk density, tapped density, Carr's compression index, Hausner ratio and angle of repose.

I) Bulk Density:

The bulk density is defined as the mass of powder divided by bulk volume. The bulk density depends on particle size, distribution, shape and cohesiveness on particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density expressed in gm/cm^3 and given by -

$$\text{Bulk density} = \frac{Mass\ of\ powder}{Bulk\ volume\ of powder}$$

II) Tapped Density:

The tapped density is defined as the mass of the powder divided by tapped volume. The quantity of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from constant height and tapped volume was read. It is expressed gm/cm^3 and given by-

$$\text{Tapped density} = \frac{Mass\ of\ powder}{Tapped\ volume\ of\ powder}$$

III) Carr's Compressibility Index (C.C.I.):

Use for compare the bulk density and tapped density. It is calculated using following equation.

$$\%\ \text{Compressibility Index} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

Relationship between % Compressibility Index and flowability,

. % Compressibility Index	Flowability
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
40>	Extremely poor

IV) Hausner's ratio:

A similar index like percentage compressibility index has been defined by Hausner. Values less than 1.25 indicate good flow, where as greater than 1.25 indicates poor flow. Added glident normally improves flow of the material under study. Hausner's ratio can be calculated

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

V) Angle of Repose (θ):

Angle of Repose is defined as the maximum angle possible between the surface and the horizontal plane. Angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely into the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation-

$$\text{Angle of Repose } (\theta) = Tan^{-1}\frac{h}{r}$$

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Where, θ= Angle of Repose,
h = Height of the heap,
r = Radius of the heap.

Relationship between Angle of Repose and flowability,

Angle of Repose (θ)	Flowability
< 25	Excellent
25-30	Good
30-40	Passable
40>	Very poor

2.1.9. Evaluation of Post-compression parameter study for Tramadol Hydrocholoride matrix tablet

I) Measurement of thickness of Tramadol Hydrochloride matrix tablet:

The thickness of tablet was measured by using screw gauge. The thickness variation should be with in ±5% limit. All the thickness was measured by screw gauge. In this screw gauge, main scale reading (MSR) = 2mm

Circular scale reading (CSR) = 64mm
Least count (LC) = 0.01
Error = 6 x 0.01 =0.06
Total thickness = [{MSR + (CSR x LC)} +0.06]

II) Tablet Hardness test of Tramadol Hydrochloride matrix tablet (lee et al., 1999, Lachman et al., 1987):

In this experiment Monsanto hardness tester determined hardness of tablets. It has a graduated scale, which gives the reading in kg / sq cm. the tablet to be tested was placed between the spindle and anvil. The desired pressure needed to hold the tablet in position was moved so that the indicator was fixed zero. The pressure was then applied till the tablet broken. The reading was noted, which indicate the pressure which was needed to break the tablet

III) Measurement of tablet friability of Tramadol Hydrochloride matrix tablet:

The friability of tablets was determined by Roche friabilator. This device subjected a number of tablets to combined effects of abrasion and shock by utilizing a plastic chamber that revolved at 25 rpm, dropping the tablets a distance of six inches with each revolution. 20 tablets were weighed and placed in the friabilator; it was operated for 100 revolutions. The tablets were then dusted and reweighed.

For the calculation,

%weight loss = initial weight of tablets (w^1) – final weight (w^2) / w^1 x 100

conventional compressed tablets loss less then 0.5 to 1.0 % of their weight are generally acceptable.

IV) Weight variation test of Tramadol Hydrochloride matrix tablet:

For each batch 20 tablets were selected randomly and their average weight was determined. Weight of the individual tablet was also determined. The tablets meet the weight variation test if not more than of the individual weights deviate from the average weight by more than the percentage shown in table below and none deviates by more than twice that percentage.

Official specification of weight variation

Average weight of tablet	Percentage deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

V) Content uniformity test of Tramadol Hydrochloride matrix tablet:

The Weight variation test is clearly not sufficient to assure uniform potency of tablets of moderate or low dose drugs, in which excipients make up the bulk of the tablet weight. To assure uniform potency for tablets of low dose drugs, a content uniformity test is applied. 30 tablets are randomly selected for sample, and at least 10 tablets are assayed individually spectrophotomerically. 9 of the 10 tablets must contain not less than 85% or more than 115%of the labeled drug content. The 10^{th} tablet may not contain not less than 75% or more then 125% of the labeled drug content. If these conditions are not met, the tablets remaining from the 30 must be assayed individually, and none may fall outside of 85 to 115%.

VI) The content uniformity test of Tramadol Hydrochloride matrix tablet was performed (as per IP, 1996) by following way:

Weighed and powered 20 tablets, weighed accurately a quantity of the powder equivalent to 0.5 g of Tramadol hydrochloride extracted with 60 ml of acetone for 15 minutes and filter. Washed the residue with three quantities, each of 10 ml, of acetone and gently evaporated the filtrate just to dryness in a current air. Dissolved the residue in 100 ml of ethanol (95%), previously neutralized to phenolphthalein solution, and titrated with O.IM sodium hydroxide using phenolphthalein solution as indicator.

VII) Disintegration test of Tramadol Hydrochloride matrix tablet:

The drug release process from tablets often includes a step at which the tablets disintegrate into smaller fragments. In our experiment the disintegration test was done by using USP disintegration test apparatus (excel, India).

To test the disintegration test three tablets of each batch was placed in 3glass tube and the basket rack was positioned in the beaker containing 900 ml of phosphate buffer pH 7.4 solution maintained at 37 ±2˚c. The disintegration time was recorded using mobile phone stop watch

2.1.10. In-vitro drug release studies

In-vitro drug release studies for the prepared matrix tablets was conducted for a period of 12 hours by using 8 station USP TDP- 08L (Electro Lab, Mumbai) apparatus was maintained at 37^0C with a stirring rate of 100 rmp speed. The in-vitro drug release study was performed in 0.1N HCl, Ph 1.2 for 2 hours and in phosphate buffer Ph 6.8 up to 12 hours. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample was analyzed at 271nm for Tramadol Hydrochloride by a UV- visible spectrophotometer. The amount of drug present in the sample was calculated in the following Table No.8.

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III. RESULT AND DISCUSSION

3.1. Pre-formulation

3.1.1. Determination of organoleptic properties:

I) Physical appearance:

Tramadol Hydrochloride is a white crystalline, odourless and bitter taste powder.

II) Determination of melting point:

The melting point of Tramadol Hydrochloride was determined by capillary method. The melting point of Tramadol Hydrochloride is 180^0C to 184^0C. It was similar to the pharmacopoeial standards.

III) Solubility:

Readly soluble in water and ethanol, 0.1 N HCl, buffer and acetone.

3.1.2. Preparation of Standard Calibration Curve

The maximum absorbance was observed at 271nm. The standard curve was found to be linear in the range of 10 µg/ml to 80 µg/ml and having the regression co-efficient value of 0.9996. Drug- excipient compatibility studies were done by FTIR –spectrophotometer. The result obtained are shown in Table No.2,3 and Figure No, 1,2.

I) Data for standard graph of Tramadol Hydrochloride in 0.1N HCl (pH 1.2) at 271nm.

Table No. 2. Absorbance data for calibration curve of Tramadol Hydrochloride in 0.1N HCl,pH 1.2.

Sl.No.	Concentration of drug in µg/ml	Absorbance at nm
1	0	0
2	10	0.0587
3	20	0.1242
4	40	0.2251
5	60	0.3341
6	80	0.4354

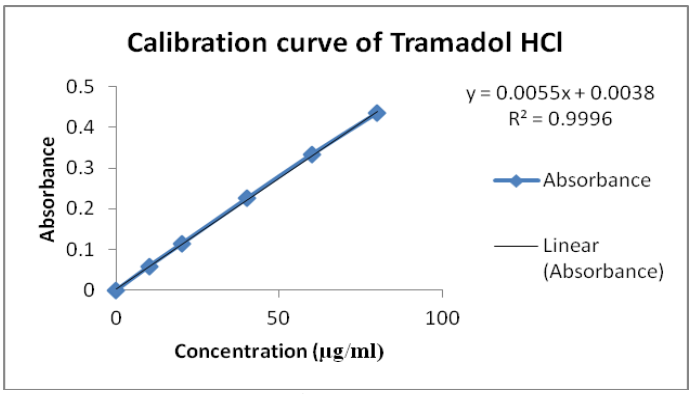

Figure No.1. Calibration curve of Tramadol Hydrochloride in 0.1N HCl,pH 1.2.

II) Data for standard graph of Tramadol Hydrochloride in 0.1N Phosphate buffer (pH6.8) at 271nm.

Table No. 3. Absorbance data for calibration curve of Tramadol Hydrochloride in 0.1N Phosphate buffer (pH6.8)

Sl. No.	Concentration of drug in µg/ml	Absorbance in nm
1	0	0
2	10	0.114
3	20	0.223
4	40	0.427
5	60	0.614
6	80	0.803

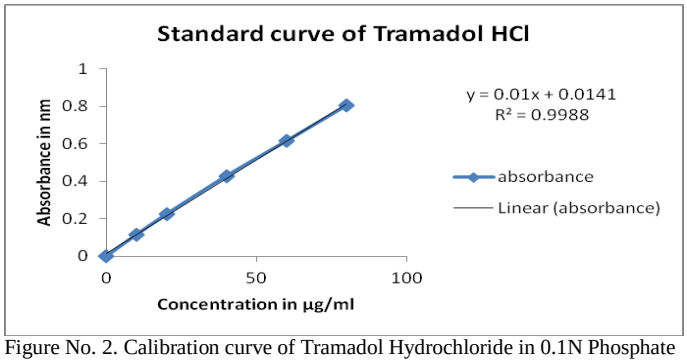

Figure No. 2. Calibration curve of Tramadol Hydrochloride in 0.1N Phosphate buffer pH 6.8

3.1.3. Compatibility studies with FTIR Spectrophotometer

The FTIR spectrum of Tramadol Hydrochloride is shown in Figure No. complies with standard functional group frequencies Table No. 4 and 5.

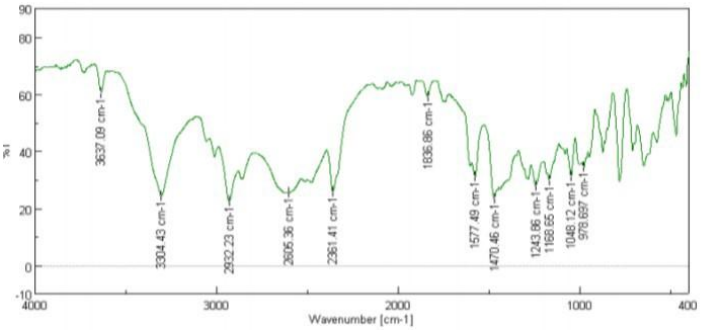

Figure No. 3. FTIR Spectra of Tramadol Hydrochloride

Table No.4. IR frequencies of Tramadol Hydrochloride

Functonal group	Characteristic wave number(cm^{-1})	Tramadol HCl observed wave number(cm^{-1})
Ar-NH_2	3540-3460	3304.43
CH asymmetric stretching	2935-2915	2932.23
Conjugated C=O	1680-1620	1677.49
CH_3 Stretching	1470-1430	1470.46

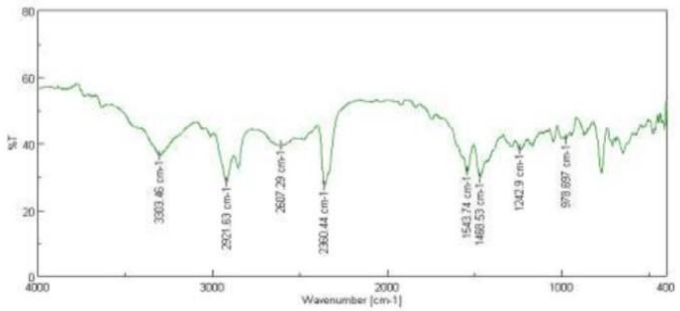

Figure No.4. FTIR Spectra of Tramadol Hydrochloride+ Acacia+ Xanthan gum + Tragacanth.

The compatibility between drug and polymer were carried out by using FTIR peak matching method. All major peak present in the spectrum of the pure drug were observed in the spectrum of drug-polymer mixture. This suggest that the drug remains in its normal structure and hence this confirmed the

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absence of any chemical interaction or complexation between drug and polymers.

Table No.5. IR frequencies of physical mixture Tramadol Hydrochloride + Acacia + Xanthan gum + Tragacanth.

Functional group	Characteristic wave number(cm^{-1})	Tramadol HCl wave number(cm^{-1})	Tramadol HCl + polymer mixture wave number(cm^{-1})
Ar-NH_2	3540-3460	3304.43	3303.46
CH asymmetric stretching	2935-2915	2932.23	2921.63
Conjugated C=O	1680-1620	1677.49	1643.74
CH_3Stretching	1470-1430	1470.46	1463.53

3.1.4. Pre-compression Parameters study for Tramadol Hydrochloride matrix tablet

The Table No.6. the granules of nine formulations (F1-F9) are evaluated for flow properties such as bulk density, tapped density, Hausner Ratio, Carr's compressibility index and angle of repose are showed that the angle of repose for granules was found to be in the range of 22.51° to 27.15° which suggest the good flow properties. Bulk density of formulation was found to be in the range of 0.341 to 0.407 gm/cm^3. The percentage of Carr's compressibility index of powder was found to be in the range below 20% indicating that the granules have good flowability and compressibility. The Hausner ratio was ranging within 1-1.2 all the formulation showed that they have good flow properties.

3.1.5. Evaluation of Post-compression parameters study for Tramadol Hydrocholoride matrix tablet

The Table No.7 shows the result of the hardness of tablets of each formulation was measured and found in the range of 5.1 to 6.1 kp for the tablets. Friability of tablets the percentage of weight loss of the tablets of each formulation was measured and found to be in the range of 0.34% to 0.48% which was under acceptable limit ie $<$1w/w. The weight verification from each batch showed uniformity of content in the range 98.93% to 100.06%. The average thickness of each batch the results of each set are within $\pm$5% deviation range.

Table No.6. Pre-compression parameters of formulations F1 to F9.

Formulation Code	Bulk density (gm/cm^3)	Tapped density(gm/ cm^3)	Hausner Ratio	Carr's Compressibility Index(%)	Angle of Repose (°)
F1	0.342	0.406	1.132	13.96	23.42
F2	0.406	0.469	1.145	12.52	22.82
F3	0.398	0.441	1.123	10.68	23.68
F4	0.354	0.413	1.145	12.72	24.64
F5	0.361	0.411	1.137	12.63	26.10
F6	0.348	0.382	1.139	11.74	27.15
F7	0.386	0.424	1.125	12.82	24.24
F8	0.341	0.394	1.144	12.52	22.51
F9	0.407	0.449	1.146	12.65	22.67

Table No.7. Post-compression parameters of formulations F1 to F9

Formulation Code	Average hardness (kp)	Friability(% w/w)	Average weight of Tablet (mg)	Average thickness(mm)	Uniformity of drug content (%)
F1	5.5	0.34	300	4.23	98.93
F2	5.3	0.38	300	4.36	99.12
F3	5.2	0.48	300	4.56	99.42
F4	5.1	0.45	301	4.39	99.46
F5	5.8	0.39	299	4.36	99.89
F6	5.7	0.42	300	4.43	99.46
F7	6.1	0.46	300	4.32	100.06
F8	5.6	0.41	301	4.45	99.56
F9	5.4	0.43	300	4.43	99.98

3.1.6. In-vitro drug release profile studies

Table No.8. Dissolution profile for Tramadol Hydrochloride against time.

Time of Hours	<---------Cumulative percentage of drug release------->								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.18	21.31	20.28	22.22	20.32	19.31	19.15	19.23	18.57
2	39.35	37.52	38.36	36.85	38.51	36.51	37.85	35.85	34.39
3	53.51	47.21	50.14	46.21	49.38	46.32	46.41	44.31	41.31
4	78.32	51.75	62.04	53.57	63.51	59.51	60.51	56.51	54.32
5	91.51	63.81	79.31	64.31	79.57	74.57	71.32	67.52	65.71
6	95.72	80.32	85.21	82.25	84.89	78.91	75.51	70.14	68.92
7	98.94	94.71	89.31	95.31	90.32	83.75	78.81	73.53	75.07
8	-	98.32	94.72	98.91	93.57	87.32	82.31	77.21	87.02
9	-	-	99.21	-	98.18	93.71	85.51	84.85	90.71
10	-	-	-	-	-	94.81	91.21	90.67	93.05

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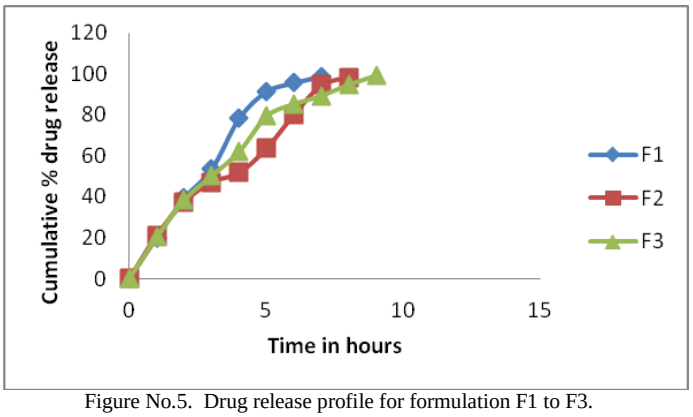

Figure No.5. Drug release profile for formulation F1 to F3.

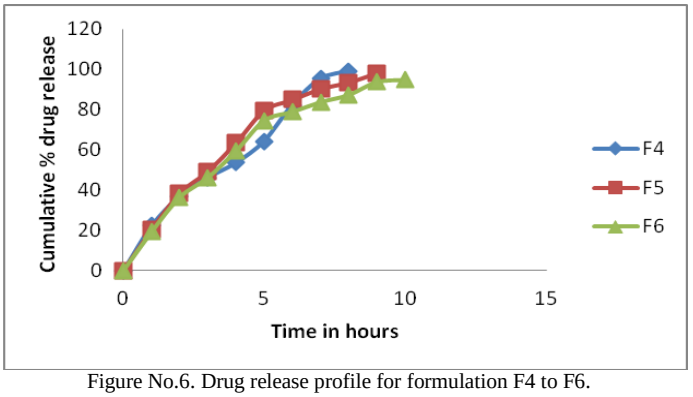

Figure No.6. Drug release profile for formulation F4 to F6.

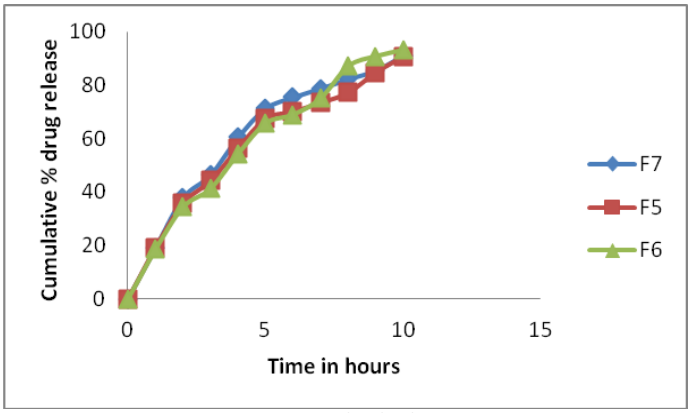

Figure No.7. Drug release profile for formulation F7 to F9.

The cumulative percentage of drug release vs time were tabulation and the graph of drug release profile were shown Table No.6 and Figure No. 5, 6 and 7. The formulation F1 to F3 Containing acacia showed drug release not more than 9 hours. Drug release rate decrease with increase in concentration of polymer. Tablets containing xanthan gum as a polymer in the formulation F4 to F6 showed drug release not more than 11 hours. Whereas formulation F7 to F9 Containing the tragacanth showed the drug release up to 12 hours. For all the polymer used the drug release rate retards with increase in the concentration of the polymer.

IV. CONCLUSION

The tablets developed showed good physiochemical properties and demonstrated satisfactory sustained drug release. Thus natural gum like as acacia, xanthan gum and tragacanth are sutable drug release rate-controlling polymers for tramadol and possibly similarly hypodermic polymer.

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