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FORMULATION DEVELOPMENT AND EVALUATION OF TAPENTADOL HYDROCHLORIDE EXTENDED RELEASE MATRIX TABLETS

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ABSTRACT

Tapentadol hydrochloride is a central analgesic used to treat moderate to severe pain, which has a biological half-life of 4 hours. The present study involves the formulation and evaluation of extended release matrix tablets of Tapentadol hydrochloride by direct compression method. Matrix systems are drug delivery systems that utilize the principle of drug release through a matrix formed by the polymer system when exposed to the body fluids /release media. These systems are versatile, easy to manufacture and cost effective since they do not involve expensive coating processes. Tapentadol hydrochloride by direct compression method using HPMC K_4M, HPMC E_5, HPMC $K_{100}LV$, Xanthangum, Chitosan, Surelease, Metalose as matrix material with lactose, starch, magnesium stearate and aerosil. Matrix tablets were evaluated by different parameters such as thickness, hardness, weight uniformity, content uniformity, in vitro drug release, *in vitro* drug permeation and FTIR studies. Optimized formulations for model drug were developed and evaluated for pharmacopoeial and non-pharmacopoeial tests. The test results were within the limits. The in vitro release studies for the developed formulations were carried out in 0.1 N HCL for 2 hours and then in pH 7 phosphate buffer for

the next preceding hours using type-I apparatus (basket) at 100 rpm. Drug release from the HPMC matrices showed that viscosity of the HPMC plays important role and in the remaining polymer matrices, the type of polymer and concentration of the polymer plays important role. The order of retardation of drug release was Xanthangum > Surelease > Chitosan > Metalose. In view of the above findings, it can be suggested that formulation containing combinations of HPMC K_4M and Xanthangum (F_6) can be employed successfully for the development of extended release matrix tablets of Tapentadol hydrochloride

KEYWORDS: Matrix tablets, Tapentadol, HPMC, Xanthan gum, Invitro Drug Release

INTRODUCTION

Matrix Tablets

Historically, it is the most popular drug delivery system, because of its low cost and ease of fabrication. Methods of altering the kinetics of drug release from the inherent first order behaviour especially to achieve a constant rate of drug release from matrix devices have involved several factors.

In this type of controlled drug delivery system, drug is homogenously dispersed in cross linked polymers to make a matrix environment. Drug release from the matrix system can occur either by dissolution or by diffusion mechanism. Methods of altering the kinetics of drug release from the inherent first order behaviour especially to achieve a constant rate of drug release from matrix devices have involved several factors. The matrix material should comply with the following conditions:

- ✓ Should be inert.
- ✓ Should be able to form stable and strong matrices when compressed either by direct compression or by dry granulation or by wet granulation method.
- ✓ Should be non-toxic.

Advantages of the matrix systems

- These are easy to manufacture in a wide range of shape and sizes.
- Economic to manufacture.
- Chances of dose dumping are less.
- Suitable for both non-degradable and degradable systems.
- High molecular weight compounds can be made to release.
- Release profile can be easily tailored.

- Reproducible release profile.
- Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release.

Disadvantages of the matrix systems

- The remaining matrix must be removed after the drug has been released.
- The drug release rates vary with the square root of time.

Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

Types of matrix tablets

1. Hydrophilic matrices
2. Fat-wax matrices
3. Plastic matrices

Examples of different types of matrices

Types of matrices	Examples
Hydrophilic matrices	Methyl cellulose, Hydroxy ethyl cellulose, Sodium carboxy methyl cellulose, carboxy poly methylene, Hydroxy propyl methyl cellulose (HPMC).
Fat-wax matrices	Stearyl alcohol, Stearic acid, Triglycerides, Carnauba wax, Poly ethylene glycol.
Plastic matrices	Polyvinylchloride, Ethyl cellulose, Methyl acrylate- methyl acrylate copolymer, Polyethylene

Requirements of matrix materials

The matrix materials must comply with the following conditions

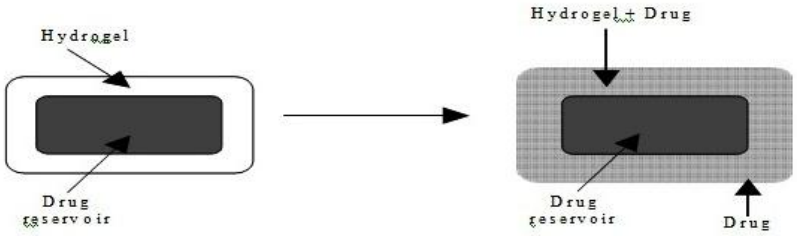
• They must be completely inert and non-reactive with the drug and additives in the tablet.

• They must be able to form stable and strong matrices when compressed either directly or more often as granules prepared by the addition of a binding agent.

• They must be non-toxic.

Hydrophilic matrix system

Drug delivery technologists usually tend to consider all hydrophilic delivery systems, as hydrogels. Hydrogels are hydrophilic macromolecular networks, after swelling they maintain their shape due to permanent links. The very high water content and special surface properties of swollen form gives them the ability to simulate natural tissues. The most widely used polymers for drug delivery control; particularly in oral applications are swellable polymers. Carboxy methyl cellulose sodium, hydroxyl methyl cellulose, polyethylene oxide, polyvinyl pyrolidone and natural gums can be used as matrix materials. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix material. On immersion in water the hydrophilic matrix quickly forms a gel layer around the tablet. Drug release is controlled by the gel diffusional barrier and /or tablet erosion.



Matrix System

In these systems, the drug is dispersed throughout the three dimensional structure of the hydrogel. Release occurs due to diffusion of the drug through the water filled pores.

hydrogel formation in reservoir systems

MATERIALS AND METHODS

Table 1: List of Materials used

-+	Material	Supplied
1	Tapentadol HCl	Gift sample from Bio – Leo analytical Lab, Prashanthi nagar
2	Lactose	Drugs India, Hyderabad
3	Starch	Drugs India, Hyderabad
4	HPMC K4M	Drugs India, Hyderabad
5	HPMC E5	Drugs India, Hyderabad
6	HPMC K100LV	Drugs India, Hyderabad
7	Xanthangum	Drugs India, Hyderabad
8	Chitosan	Drugs India, Hyderabad
9	Surelease	Drugs India, Hyderabad

10	Metalose	Drugs India, Hyderabad
11	Magnesium stearate	Drugs India, Hyderabad
12	Aerosol	Drugs India, Hyderabad

Table 2: List of Equipments used

S.No	Equipment	Manufacturer
1.	Electronic weighing balance	METTLER TOLEDO USA
2.	Mechanical sieve shaker	Retsch Solutions in Milling & Sieving GERMANY
3.	pH meter	WTW Ino labs, Texas
4.	Dissolution apparatus	ELECTROLAB MUMBAI
5.	UV-visible spectrophotometer	SHIMADZU Solutions for Science since 1875 JAPAN
6.	Tapped Density Tester USP	ELECTROLAB MUMBAI
7.	Vernier caliper	Mitutoyo www.mitutoyo.com
8.	Friabilator	ELECTROLAB MUMBAI
9.	Hardness tester	Schleuniger To Be Precise.
10.	Tablet compression machine	cadmach® Leaders in Pharma Machinery

Formulation data for Tapentadol HCl Extended release Matrix tablets

Table 3: All weights were taken in mg per tablet.

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Tapentadol HCl	100	100	100	100	100	100	100	100	100	100	100	100
Lactose	45	45	45	45	45	45	45	45	45	45	45	45
Starch	40	40	40	40	40	40	40	40	40	40	40	40
HPMC K_4M	50	-	-	30	30	30	30	30	30	30	30	30
HPMC E_5	-	50	-	30	-	-	-	-	-	-	-	-
HPMC $K_{100}LV$	-	-	50	-	30	-	-	-	-	-	-	-
Xanthangum	-	-	-	-	-	50	30	-	-	-	-	-
Chitosan	-	-	-	-	-	-	-	50	-	-	-	-
Surelease	-	-	-	-	-	-	-	-	50	30	-	-
Metalose	-	-	-	-	-	-	-	-	-	-	50	30
Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
Total tablet weight	250	250	250	250	250	250	250	250	250	250	250	250

Preparation of Matrix release tablets

The Matrix release tablets were prepared by direct compression method.all the ingridients were mixed in formulated proportion and lubricants was added and punched using 16 station punch tablet compression machine. Each tablet contained 100 mg of Tapentadol HCl the batch size for each formulation was 50 tablets.

Table no.4 Evaluation of physical parameters of Tapentadol HCl ER Tablets

Evaluation of physical parameters of Tapentadol HCl ER Tablets						
Tablet Formulation code	**Weight of the tablet**	**Weight variation**	**Hardness (kg/cm^2)**	**Friability (%)**	**Thickness (mm)**	**Drug Content (%)**
F_1	251	250 ± 5%	6.4	0.72	2.6	99.28
F_2	249	250 ± 5%	6.3	0.68	2.6	97.16
F_3	247	250 ± 5%	6.7	0.69	2.4	101.1
F_4	250	250 ± 5%	7.1	0.65	2.36	99.5
F_5	250	250 ± 5%	6.8	0.7	2.59	99.6
F_6	252	250 ± 5%	6.6	0.66	2.45	97.68
F_7	247	250 ± 5%	6.7	0.52	2.58	97.06
F_8	246	250 ± 5%	6.7	0.68	2.4	99.41
F_9	248	250 ± 5%	6.9	0.65	2.38	98.12
F_{10}	249	250 ± 5%	6.7	0.68	2.6	98.4
F_{11}	251	250 ± 5%	6.8	0.67	2.36	102.6
F_{12}	248	250 ± 5%	6.5	0.59	2.62	97.68

***In- Vitro* Drug Release Study**

The influence of technologically defined condition and difficulty in simulating *in- vivo* conditions has led to the development of a number of *in- vitro* release methods for buccal formulations, however, no standard method has yet been developed. *In-vitro* release rate of buccoadhesive tablets of Metoclopramide Hydrochloride was carried out using rotating basket apparatus (USP Type I). The dissolution medium consisted of 500 ml of phosphate buffer (pH 6.8). The release study was performed at 37 ^{0}C ± 0.5 ^{0}C with a rotation speed of 50 rpm. The sample (5 ml) was withdrawn at time interval of 30, 60 and 90 minutes up to 10 h and replaced with 5 ml of dissolution media. The amount of Linagliptin released was determined spectrophotometrically at 262 nm.

Table 5: Parameters were used for the dissolution study

Apparatus	**USP Dissolution apparatus (Type I)**
Dissolution medium	Phosphate buffer (pH 6.8)
Temperature	37±0.5 °C
Volume	500 ml
Speed	50 rpm

Sample withdrawn	5 ml
Running Time	8 hrs

Stability Study

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

Formulations were selected for stability on the basis of the In-vitro drug release profile. The formulations were subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines i.e. 25^0C/60% RH and 40^0C/75% RH in air tight high density ethylene bottles for 2 months in thermostated ovens. Tablets were evaluated for the different physicochemical parameters i.e. content uniformity, weight variation, bioadhesive strength, surface pH, swelling study, and percentage of drug release.

RESULTS AND DISCUSSION

Table 6: Organoleptic Properties

Colour	**White**
Odour	Odorless
Taste	Tasteless
Appearance	Crystalline powder

Table 7: Solubility Study

Name of solvent	**Parts of solvent required per part of solute**	**Solubility**
Distilled water	0.8	Very Soluble
Methanol (95%)	3	Freely soluble

STANDARD CURVE OF TAPENTADOL HCl

Table 8: Calibration Curve data of Tapentadol HCl in 0.1 N HCl buffer.

S.NO	**CONCENTRATION (µg / ml)**	**ABSORBANCE**
1	0	0
2	2	0.123
3	6	0.376
4	10	0.584
5	14	0.818
6	18	01.037

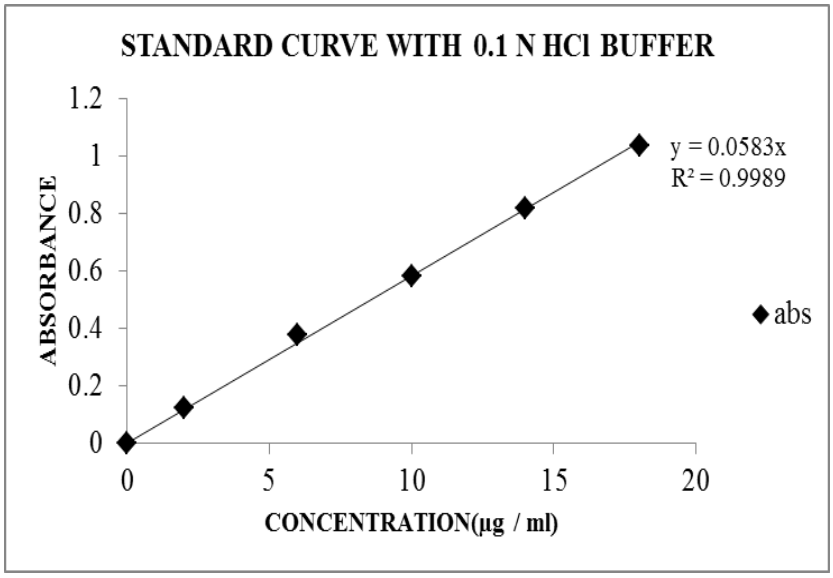


Figure no.1 Standard Curve of Tapentadol HCl in 0.1 N HCl buffer

Table no.9 Calibration Curve data of Tapentadol HCl in pH 7 phosphate buffer

S.NO	COCENTRATION (µg / ml)	ABSORBANCE
1	0	0
2	2	0.11
3	6	0.285
4	10	0.425
5	14	0.632
6	18	0.778
7	22	0.981

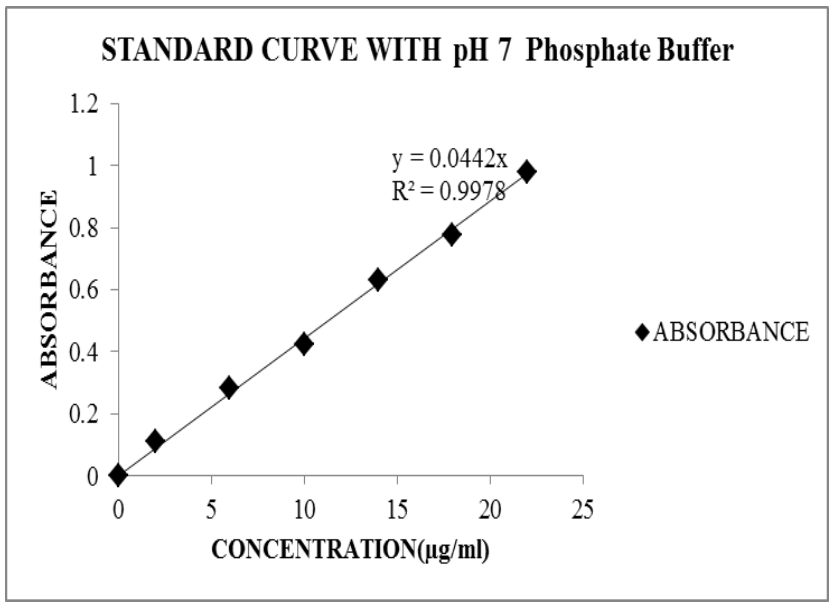


Figure no: 2 Standard Curve of Tapentadol HCl in pH 7 Phosphate buffer Drug excipient compatibility studies.

PURE DRUG

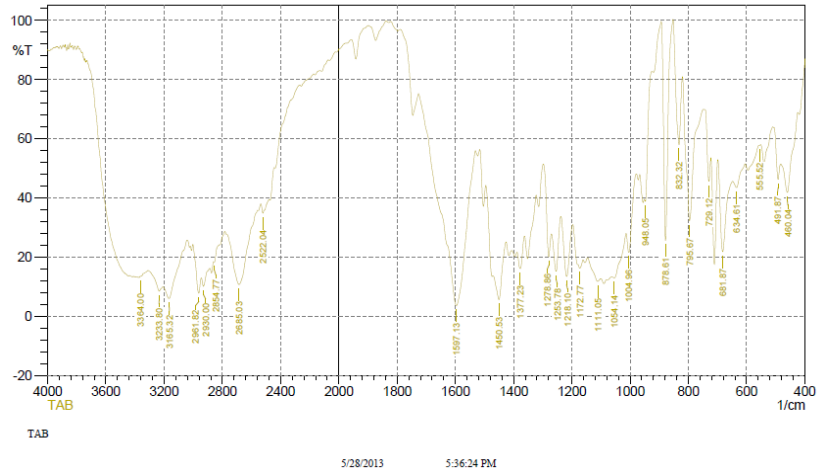


Figure no.3: IR spectra of pure drug

DRUG WITH HPMC K_4M

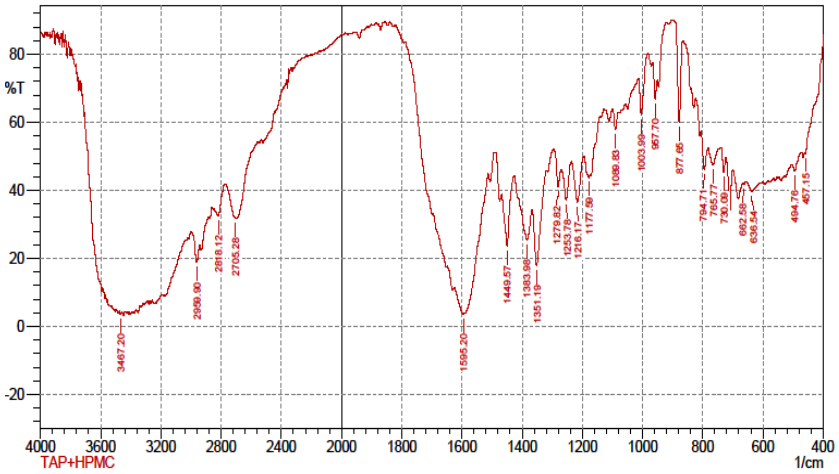


FIGURE no.4: IR spectra of drug + HPMC K_4M

DRUG WITH CHITOSAN

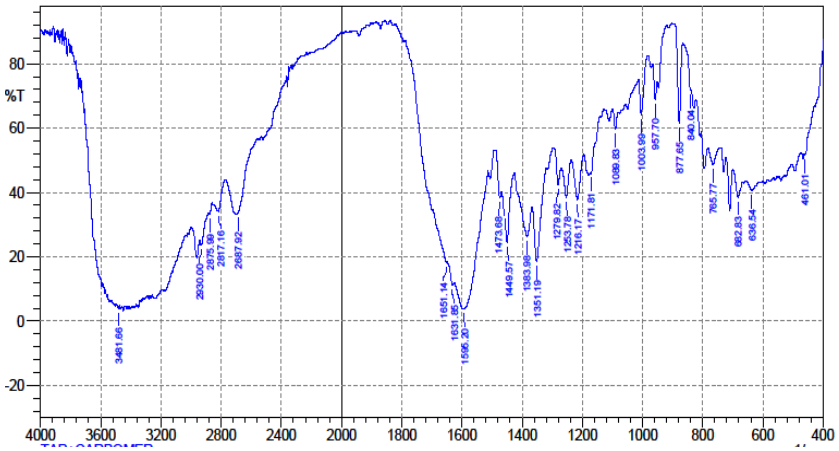


FIGURE no.5: IR spectra of drug + Chitosan

DRUG WITH SURRELEASE

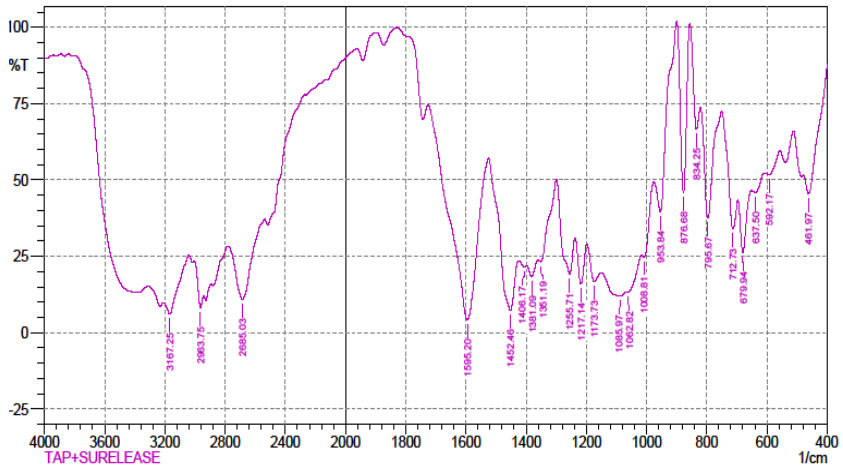


FIGURE no.6: IR spectra of drug + Surrelease

λ_{max} of Tapentadol HCl

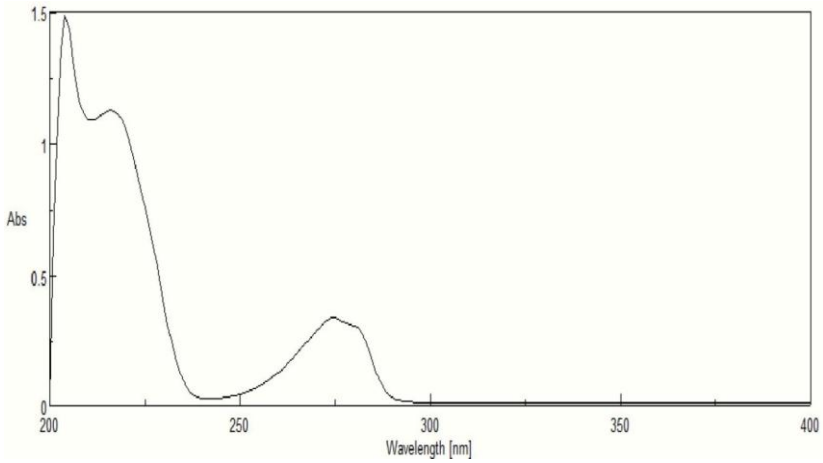


Figure no.7: Spectrum showing the λ_{max} of the Tapentadol HCl

Table 10: Micromeritic Properties of Powder Blend

Micrometric properties of Tapentadol powder blend						
S.No	**Powder blend**	**Angle of repose (θ) (º)**	**Loose bulk density (LBD) (gm./ml)**	**Tapped bulk density (TBD) (gm./ml)**	**Carr's compressibility index (%)**	**Hausner's ratio**
1	F_1	34.2 ± 0.4	0.52	0.65	20.02	1.25
2	F_2	35.5 ± 0.5	0.55	0.64	26.21	1.16
3	F_3	33.2 ± 0.5	0.49	0.57	14.04	1.163
4	F_4	32.1 ± 0.8	0.53	0.61	13.11	1.15
5	F_5	31.8 ± 0.3	0.53	0.66	19.69	1.24
6	F_6	32.4 ± 0.4	0.48	0.55	12.72	1.14
7	F_7	33.1 ± 0.3	0.52	0.65	20	1.25
8	F_8	33 ± 0.6	0.5	0.58	13.79	1.16
9	F_9	32.1 ± 0.7	0.53	0.61	13.11	1.15
10	F_{10}	35.4 ± 0.2	0.51	0.65	21.53	1.27

11	F_{11}	33.5 ± 0.3	0.49	0.55	10.9	1.12
12	F_{12}	32.5 ± 0.4	0.54	0.61	11.47	1.12

Table 11: Evaluation studies of Tapentadol HCl ER Tablets

Evaluation of physical parameters of Tapentadol HCl ER Tablets						
Tablet Formulation code	**Weight of the tablet**	**Weight variation**	**Hardness (kg/cm^2)**	**Friability (%)**	**Thickness (mm)**	**Drug Content (%)**
F_1	251	250 ± 5%	6.4	0.72	2.6	99.28
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F_6	252	250 ± 5%	6.6	0.66	2.45	97.68
F_7	247	250 ± 5%	6.7	0.52	2.58	97.06
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F_{10}	249	250 ± 5%	6.7	0.68	2.6	98.4
F_{11}	251	250 ± 5%	6.8	0.67	2.36	102.6
F_{12}	248	250 ± 5%	6.5	0.59	2.62	97.68

Where, All values are mean ±S.D,n=20

DISSOLUTION STUDIES

Table no.12: *In Vitro* dissolution Data of Formulations F_1 to F_3

Time (hours)	Amount of drug released		
	F_1	F_2	F_3
0	0	0	0
1	3.6	10.5	5.4
2	3.7	21.4	9.5
3	9.7	45.3	15.7
4	13.6	58.7	39.3
5	30.6	74.5	56
6	42.3	99.6	65.6
7	49.2		86.7
8	58.7		
9	68.2		
10	74.6		
11	85.1		
12	95.2		

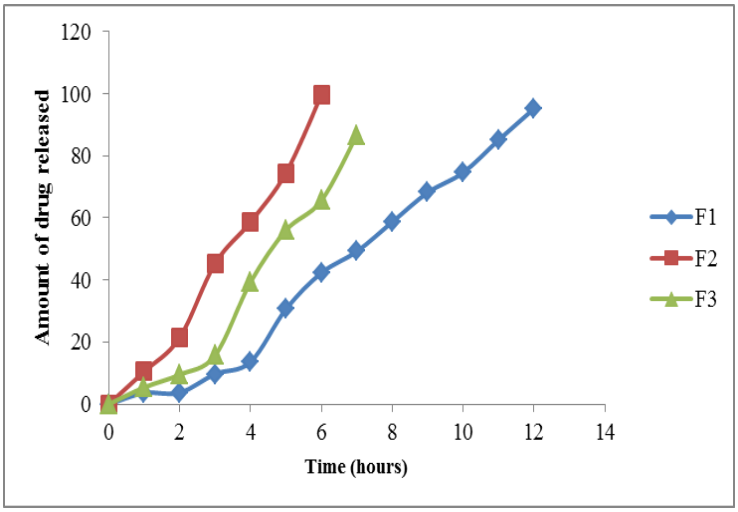

Figure no.8: *In Vitro* dissolution plot for the Formulations F_1 to F_3

Table no.13: *In Vitro* dissolution Data of Formulations F_4 and F_5

Time (hours)	Amount of drug released	
	F_4	F_5
0	0	0
1	9	33.8
2	14.9	35
3	20.1	51.8
4	31.5	62.3
5	45.4	81.9
6	50.2	87.8
7	58.7	91
8	73.5	96.3
9	83	
10	87.3	
11	89.4	

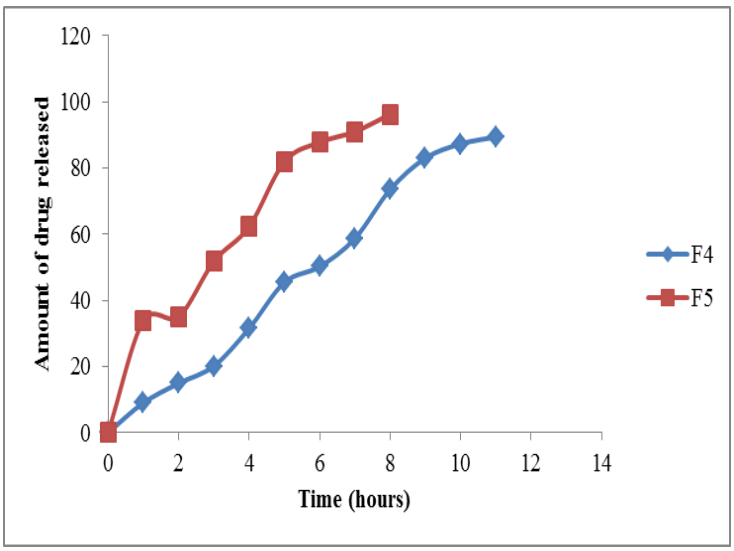

Figure no.9: *In Vitro* dissolution plot for the Formulations F_4 and F_5

Table 14: *In Vitro* dissolution Data of Formulations F_6 to F_8

Time (hours)	Amount of drug released		
	F_6	F_7	F_8
0	0	0	0
1	2.5	2.4	3.1
2	5.9	9.4	6.4
3	11.8	15.1	12.8
4	16.4	25.9	20.7
5	21.8	31.2	27.1
6	31.3	40.8	36.9
7	37.3	47.5	41.7
8	42.1	58.6	50.4
9	46.7	63.4	55.7
10	55.6	70.4	63.5
11	64.2	75.5	72.6
12	68.7	80.1	76.4

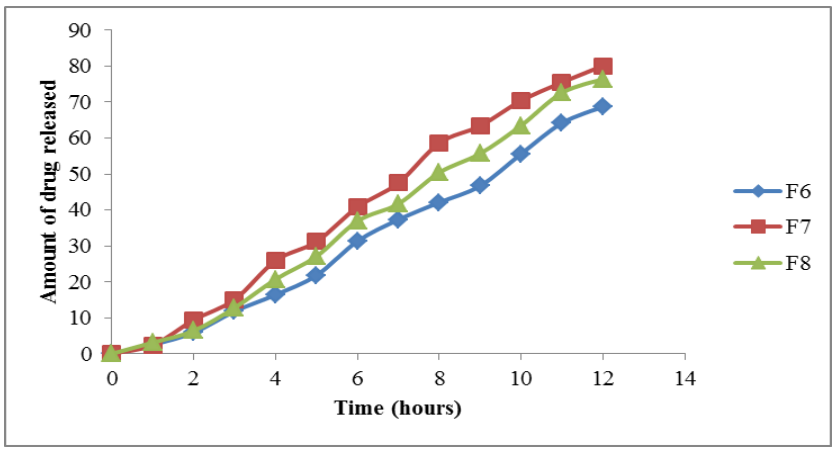

Figure no.10: *In Vitro* dissolution plot for the Formulations F_6 to F_8

Table no.15: *In Vitro* dissolution Data of Formulations F_9 to F_{12}

Time (hours)	Amount of drug released			
	F_9	F_{10}	F_{11}	F_{12}
0	0	0	0	0
1	1.9	3.8	4.3	8.9
2	4.3	8.2	6.6	11.8
3	9.8	16.5	10.2	24.4
4	14.6	23.1	28.6	35.7
5	20.1	34.9	40.5	47
6	30.5	40.6	43.8	53.4
7	35.2	52.1	50.8	66.1
8	43.6	57.9	61.8	81.9
9	52.9	68.3	69.8	88.9
10	57.8	75.6	74.6	90.4
11	67.3	81.3	77.8	90.5
12	72.1	84.4	88.8	90.5

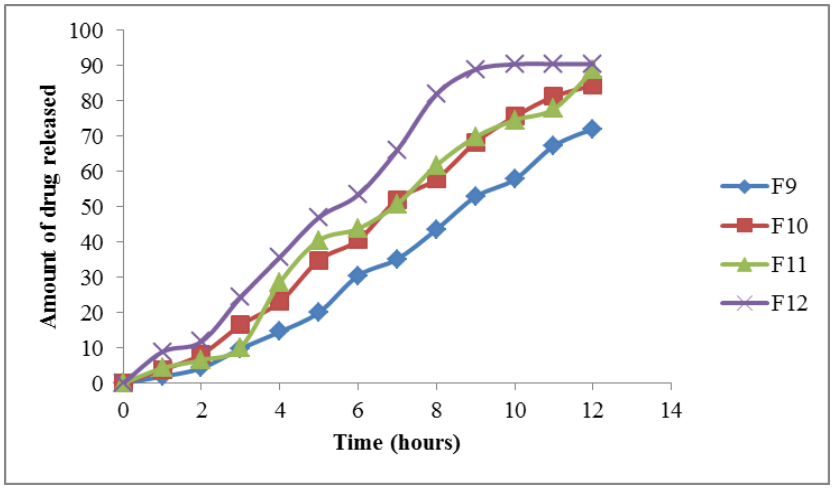

Figure no.11: *In Vitro* dissolution plot for the Formulations F_9 to F_{12}

First – order release profile:

Table no.16: Log % of Drug Unreleased Vs. Time plots for Formulations F_6

Time (hours)	% of drug released
	F_6
0	2
1	1.989005
2	1.97359
3	1.945469
4	1.922206
5	1.893207
6	1.836957
7	1.797268
8	1.762679
9	1.726727
10	1.647383
11	1.553883
12	1.495544

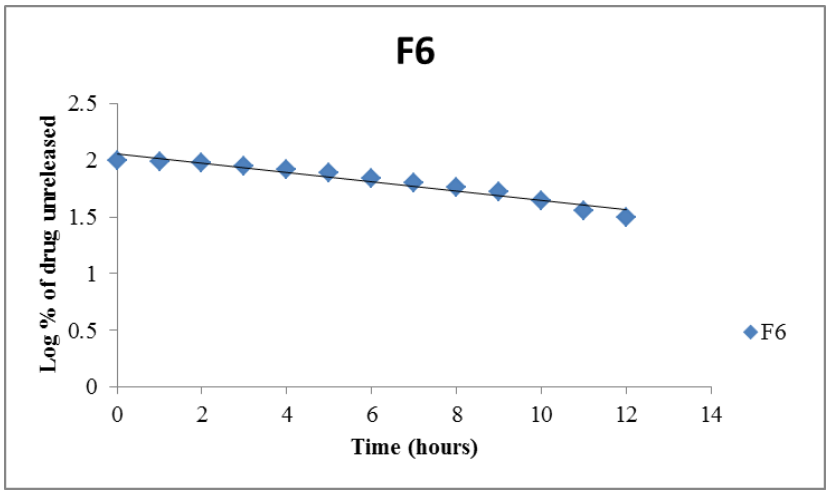

Figure no.12: First order plots for the batches F_6 Higuchi release profile.

Table no.17: Higuchi plots for formulations F_6

SQRT Time	% of drug released F_6
0	0
1	2.5
1.414	5.9
1.732	11.8
2	16.4
2.2360	21.8
2.4494	31.3
2.6457	37.3
2.8284	42.1
3	46.7
3.1622	55.6
3.3166	64.2
3.4641	68.7

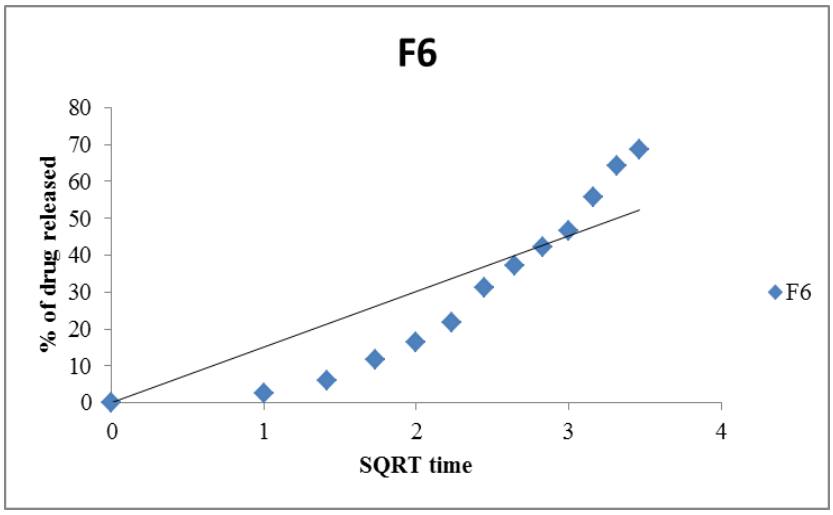

Figure no.13: Higuchi kinetic profile for the batches F_6

Korsmeyer & Peppas release profile

Table no.18: Peppas kinetics plots for the formulations F_6

Log time	Log % of drug released F_6
0	0.39794
0.3010	0.770852
0.4771	1.071882
0.6020	1.214844
0.6989	1.338456
0.7781	1.495544
0.8450	1.571709
0.9030	1.624282
0.9542	1.669317
1	1.745075

1.0413	1.807535
1.0791	1.836957

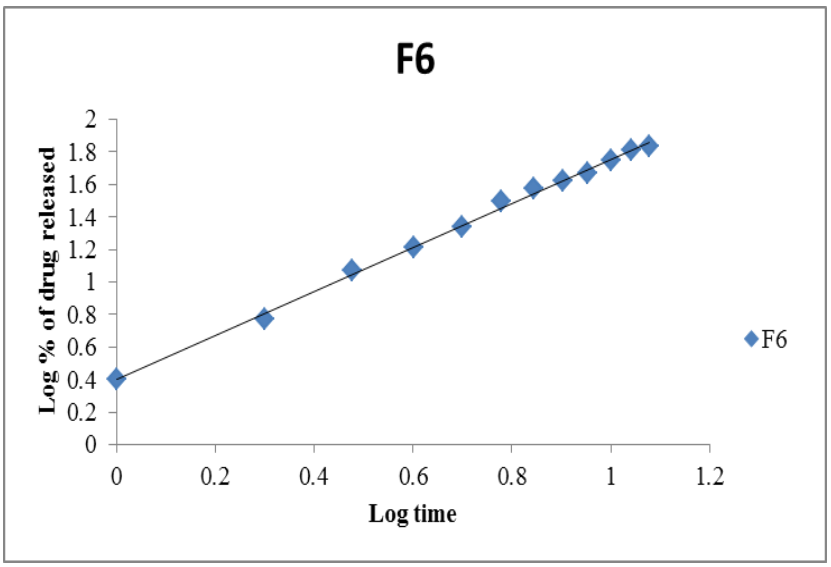

Figure no.14: Korsmeyer & Peppas kinetics profile for the batches F_6

DISCUSSION

Tapentadol hydrochloride is a central analgesic used to treat moderate to severe pain, which has a biological half – life of 4 hours. In the present study, an attempt was made to prepare extended release matrix tablets of Tapentadol hydrochloride by direct compression method using HPMC K_4M, HPMC E_5, HPMC $K_{100}LV$, Xanthangum, Chitosan, Surelease, Metalose as matrix material with lactose, starch, magnesium stearate and aerosil as co – excipients to release drug in a controlled fashion.

Matrix systems are drug delivery systems that utilize the principle of drug release through a matrix formed by the polymer system when exposed to the body fluids /release media. These systems are versatile, easy to manufacture and cost effective since they do not involve expensive coating processes.

λ_{max} of 275 was identified for Tapentadol hydrochloride in both 0.1 N HCL and p^H 7.0 Phosphate buffer by using UV – Visible Spectrophotometer. By performing compatibility studies with IR no interactions were found between drug and its admixture. Prior to compression, the powder blend was evaluated for micrometric properties such as angle of repose, bulk density, tapped density, Compressibility index and Hausner's Ratio.

The matrix tablets of Tapentadol hydrochloride were prepared by direct compression method. It is suitable for drugs which have poor flow ability. The prepared matrix tablets were evaluated for hardness, friability, weight variation, drug content, *in – vitro* drug release, drug polymer interaction.

Optimized formulations for model drug were developed and evaluated for pharmacopoeial and non-pharmacopoeial tests. The test results were within the limits. The in vitro release studies for the developed formulations were carried out in 0.1 N HCL for 2 hours and then in pH 7 phosphate buffer for the next preceding hours using type-I apparatus (basket) at 100 rpm.

The IR spectrum of Tapentadol hydrochloride pure and its physical admixture shows the good compatibility between drug and polymers.

The tablets which were prepared by the combination of HPMC K_4M with Xanthangum, Surelease, Chitosan and Metalose shows retardation in the drug release rate. Increase in the concentration of polymer (Xanthangum, Surelease, Chitosan, and Metalose) retards the drug release rate.

Drug release from the HPMC matrices showed that viscosity of the HPMC plays important role and in the remaining polymer matrices, the type of polymer and concentration of the polymer plays important role. The order of retardation of drug release was Xanthangum > Surelease > Chitosan > Metalose.

Overall, the curves fitting into various kinetic models confirmed that in – vitro release kinetics of all formulations (except F_5) were fitted into Zero order and Higuchi model.

The “n” values more than 0.5 indicates that the mechanism in which the drug release from matrices follow non – Fickian diffusion mechanism.

The “n” values less than 0.5 indicates that the mechanism in which the drug release from matrices follow Fickian diffusion mechanism.

The “n” values more than 1 indicates that the mechanism in which the drug release from matrices follow Super case II transport mechanism.

CONCLUSION

- Extended release matrix tablets of Tapentadol hydrochloride were successfully formulated using different rate controlling polymers as the retardants by direct compression method.
- Before preparing the tablets, the powder blend was evaluated for micrometric properties like angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio.
- All the prepared formulations were evaluated for thickness, hardness, friability, weight variation and *in – vitro* release.
- The physical parameters and micrometric properties of all the formulations were within the range.
- By comparing the dissolution studies of all the 12 formulations, the drug release was highly extended in F_6. Only 68 % of the drug was released within 12 hrs. The micrometric properties like Angle of repose, LBD, TBD, Carr's compressibility index, & Hausner's ratio and physical parameters like weight variation, hardness, friability, thickness & drug content were found to be within the limits. Its half – life was found to be 9.24 hrs.
- In view of the above findings, it can be suggested that formulation containing combinations of HPMC K_4M and Xanthangum (F_6) can be employed successfully for the development of extended release matrix tablets of Tapentadol hydrochloride.
- By studying the kinetic studies of drug release F_6 follows Zero order release by diffusion mechanism. Its 'n' value was less than 0.5 indicates that the mechanism in which the drug release from matrices follow Fickian diffusion mechanism.

BIBLIOGRAPHY

1. M. Diarraa, G. Pourroyb, C. Boymondc, D. Musterd, Fluoride controlled release tablets for intrabuccal uses, Biomaterials, 2003; 1293–1300.
2. John 0. Parker, Md Karen A.vankoughnett, RN, and Bernice farrel, RN Comparison of Buccal Nitroglycerin and Oral lsosorbide Dinitrate for Nitrate Tolerance in Stable Angina Pectoris. The American journal of cardiology, 1985; 56.
3. Mona Darwish, Ehab Hamed and John Messina Fentanyl Buccal Tablet for the Treatment of Breakthrough Pain: Pharmacokinetics of Buccal Mucosa Delivery and Clinical Efficacy Perspectives in Medicinal Chemistry, 2010; 4.

4. P. D. Nakhat, A. A. Kondawar, L. G. Rathi, and P. G. Yeole Development and In Vitro Evaluation of Buccoadhesive Tablets of Metoprolol Tartrate Studies, International journal of pharmaceutics February, 2009; 26-53.
5. A. Madgulkar, S. Kadam, and V. Pokharkar development of Buccal Adhesive Tablet with Prolonged Antifungal activity: Optimization and ex vivoDeposition Studies, International journal of pharmaceutics, 2009; 65-98.
6. Calum R. Park, Dale L. Munday, Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy International Journal of Pharmaceutics, 2002; 215–226.
7. Han-Gon Choia, Chong-Kook Kim, Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva, Journal of Controlled Release, 2000; 397–404.
8. Hemant H. Alur, S. Indiran Pather, Ashim K. Mitra, Thomas P. Johnston, Transmucosal sustained-delivery of chlorpheniramine maleate in rabbits using a novel, natural mucoadhesive gum as an excipient in buccal tablets, International Journal of Pharmaceutics, 1999; 1–10.
9. B. Rambali, L. Baert b. Jans, D.L. Influence of the roll compactor parameter settings and the compression pressure on the buccal bio-adhesive tablet properties International Journal of Pharmaceutics, 2001; 220: 129–140.
10. C. Narendra , M.S. Srinath , B. Prakash Development of three layered buccal compact containing metoprolol tartrate by statistical optimization technique, International Journal of Pharmaceutics, 2005; 102–114.
11. Syed Amezuddin Azhar, Putta Rajesh Kumar, Vivek Sood and Somashekar shyale studies on directly compressed Ondansetron hydrochloride mucoadhesive buccal tablets using gelatin, chitosan and xanthan gum along with hpmc k4m. Journal of applied pharmaceutical science, 2012; 02(05): 100-105.
12. Vinod KR, Rohit Reddy T, Sandhya S, David Banji, Venkatram Reddy B. Critical Review on Mucoadhesive Drug Delivery Systems. Hygeia. J.D. Med., 2012; 4(1).
13. Riya Das, Kazi Asraf Ali, Amal Kumar Bandyopadhyay Mucoadhesion and Mucoadhesive tablets-A Review. Int J Pharm Sci Tech., 2011; 6.
14. Sowjanya Battu1, K.Rajeswar Dutt, K.Jyothshna Devi , K.Maha Lakshmi, Meenu Singh Formulation and characterization of mucoadhesive bilayered tablets of diclofenac sodium using various polymers. Journal of Pharmacy Research, 2011; 4(11): 4184-4186.

15. Rohini S. Kharwade, Neha S.V Yavhare, Sachin M. More, Formulation of mucoadhesive tablet by using aegle marmelos gum. International Journal of Applied Biology and Pharmaceutical Technology, 2011; 2.
16. B.Srinivas, Chandan Mohanty, Pritosh Pattanaik, Ravi Naik, Chandan Brahma, Design and in-vitro evaluation of muco- adhesive buccal tablets of salbutamol sulphate. International journal of pharmacy and biological sciences, 2011; 1(3): 240-245.