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Research Article

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Formulation and Evaluation of Bilayer Tablet of Tramadol Hydrochloride and Diclofenac Sodium

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ABSTRACT

The aim and objective of present study is to formulate and evaluate the bilayer tablet containing Tramadol Hydrochloride immediate release layer and Diclofenac Sodium sustain release layer in order to produce a single tablet containing two different classes of drugs. Which are used to treat severe and moderately severe pain. Diclofenac Sodium and Tramadol Hydrochloride, resulting peripheral and central analgesia a "balanced analgesia" used in wider spectrum of pain management and which results in synergistically enhanced analgesic action, cost effectiveness and reduces the undesired symptoms. Tramadol Hydrochloride (IR Layer provide shorter analgesia onset (t-max) and Diclofenac Sodium (SR Layer) provide analgesic action for prolong duration. In which Immediate release layer of Tramadol Hydrochloride was prepared by wet granulation technique using sodium starch glycolate, crospovidone and croscarmellose sodium as a super disintegrants. The sustained release layer of Diclofenac Sodium was prepared by wet granulation technique using hydrophilic matrix polymers like HPMC K4 M, HPMC K15M, and HPMC K100M. Formulated bilayered tablets were evaluated for different parameters like hardness, thickness, weight variation, friability, and disintegration time and % cumulative drug release.

Key words: Bilayer tablet, hydrophilic polymer, superdisintegrant, Diclofenac sodium, Tramadol hydrochloride

Introduction

Tramadol is an centrally acting synthetic analgesic (μ-opioid receptor agonist) used to treat severe and moderately severe pain. Diclofenac sodium nonsteroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic reducing pain in certain conditions.

Combination produces a synergistically enhanced analgesic action and reduces the undesired symptoms. Provide shorter analgesia onset(t-max) and prolong duration. Diclofenac and tramadol, resulting peripheral and central analgesia a "balanced analgesia" used in wider spectrum of pain management. Treatment of moderate to severe pain, the World Health Organization (WHO) recommends combining opioid analgesics with non-steroidal analgesics in order to produce a more effective pain relief and possibly reduce amounts of analgesic which are necessary to administer.By combination with the immediately released active substance Tramadol HCl for a rapid pain relief can be achieved. The slow release of Diclofenac sodium from the retarded form permits the maintenance of therapeutic blood level over an extended time.

Bilayer tablet is new era for developing a combination of two or more active pharmaceutical ingredient in single dosage form, Promoting patient convenience and compliance. Two or more ingredient to be formulated together inspite of active having different physico-chemical characteristics (active incompatibility). Dual release tablet is a unit compressed tablet dosage form intended for oral application. It contains 2 layers in which 1 layer having conventional or immediate release part of single or multiple actives; another layer is sustained or controlled release part of single or multiple actives. They are also called as multi-layer matrix tablet. HPMC is the mostly used non ionic water soluble polymer showing pH independent and desired drug release profiles for a wide range of drugs, provide robust formulation, global availability, cost-effective manufacture. HPMC is typically used as the primary polymer, and other approved polymer have been added to enhance functionality and as a tool to modulate the drug release profile. Disintegration of the tablets by increasing water penetration and dispersion of the matrix. Here, in this study cross povidone, croscarmellose sodium, sodium starch glycolate were used a superdisintegrants and were evaluated for their effect on dissolution and disintegration of tramadol hydrochloride layer.[1-5]

Materials and Methodology

Tramadol hydrochloride and Diclofenac sodium were obtained as gift samples from (Mercury Labs, vadodara, India). HPMC K100M,HPMC K4M,HPMC K15M, microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, crosspovidone, magnesium stearate, Talc,isopropyl alcohol, were collected from loba chem. Vadodara.The bilayer tablets of diclofenac sodium and tramadol hydrochloride were developed in two stages. Blends of immediate release layer of tramadol hydrochloride and sustained release layer of diclofenac sodium were prepared separately. The individual layers were optimized based on the in vitro dissolution data and bilayer tablets were prepared by using the optimized formulae.[6]

Preformulation:

Preformulation studies were conducted for both drugs Tramadol Hydrochloride and Diclofenac sodium. For both the drugs preformulation characteristics like Description, Solubility, Melting point, Bulk density, Tapped density, Angle of repose, Hausner's ratio, Compressibility index were performed. IR absorption spectrum of Tramadol hydrochloride and Diclofenac sodium were recorded using potassium bromide (KBr) pellet method. Assay was performed for both the drugs by following respective methods given in the pharmacopoeias.[7]

Assay of Tramadol Hydrochloride.[8]

1. Dissolve 0.18 g in 25 ml of anhydrous acetic acid and add 10 ml of acetic anhydride. Titrate with 0.1 Mperchloric acid, determining the end-point potentiometrically .Carry out a blank titration.
2. 1 ml of 0.1 M perchloric acid is equivalent to 0.02998 g of Tramadol Hydrochloride.
3. Tramadol Hydrochloride Assay-95-105%.

Assay of Diclofenac sodium.[9]

1. Dissolve about 450 mg Diclofenac Sodium accurately weighed in 25 ml glacial acetic acid and titrate with 0.1 N perchloric acid,Determine the end point Potentiometrically, Perform blank determination.
2. Each ml 0f 0.1 N Perchloric acid is equivalent to 31.81mg of Diclofenac Sodium.
3. Diclofenac Sodium Assay – 90-110%

Drug Excipient Compatibility:

The compatibility of drugs with their respective excipients was studied by FT-IR spectroscopy. The scanning was performed at scanning speed 2 mm/sec with resolution of 4 cm-1 over the region 4000-400 cm-1. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction.[10]

Formulation and Development of Diclofenac sodium sustain release Layer:
The dose of Diclofenac sodium for sustained release was taken as 75 mg. Diclofenac sustained release layer tablets were prepared by wet granulation. Appropriate quantities of Diclofenac sodium and excipients like HPMC K100 M, HPMC K4M, HPMC K15M, PVP K 30 and Microcrystalline cellulose were measured accurately and all the measured powders were sifted through Seive no # 40. The above sifted materials were mixed rapidly for 5 min and again passed through sieve no 40. Iso Propyl Alcohol having 2% w/v amount of PVP K- 30 was used as the granulating liquid and the solution was added to the mixture in step 2 and was k neaded for 2-5 min, then the kneaded mass was passed through sieve no # 20 to obtain the granules.

The granules obtained in step 3 were dried in a tray drier at 50°C for 2 hrs. The dried granules were lubricated uniformly with weighed quantities of magnesium stearate and talc. The above granules were compressed into tablets by tablet compression machine. In Batch D1 to D3, HPMC K4M was used as the sustained release polymer and in Batch D4 & D5 HPMC K 15 M was used and in D6 – D8 HPMC K100M was used as Polymer.[11-12]

Formulation and Development of Tramadol Hydrochloride Immediate Release Layer:
Tramadol Hydrochloride immediate release layer tablets were prepared by wet granulation method and other excipients like microcrystalline cellulose, cross povidone, croscarmellose sodium, sodium starch glycolate were sifted through sieve no 40 #. The sifted powders were thoroughly mixed for approximately 5 min and again passed through sieve no 40 # for maintaining uniformity in particle size. Iso Propyl Alcohol having 2% w/v amount of PVP K- 30 was used as the granulating liquid and the solution was added to the mixture in step 2 and was kneaded for 2-5 min, then the kneaded mass was passed through sieve no # 20 to obtain the granules.

The granules obtained in step 3 were dried in a tray drier at 50°C for 2 hrs. The dried granules were lubricated uniformly with weighed quantities of magnesium stearate and talc. The above granules were compressed into tablets by tablet compression machine.For Batches T1 to T3 Sodium starch gylycolate, T4 to T6 Cross povidone and in T7 to T9 Croscarmellose sodium were used as superdisintegrants.[13-14]

Evaluation of the Blends:
The Tramadol Hydrochloride blend and Diclofenac sodium blend were evaluated for various pre compression parameters like Angle of repose, Bulk density, Tapped density, Carr's index, Hausner's ratio etc.[15-16]

Evaluation of the compressed tablets :
Both Tramadol Hydrochloride and Diclofenac Sodium tablets were evaluated for post compression parameters like hardness, weight variation, friability, drug content uniformity etc. The Diclofenac sodium SR tablets were evaluated for in vitro dissolution study. Tramadol hydrochloride tablets were evaluated for in vitro disintegration study and in vitro dissolution study. From the in vitro dissolution study best formulations were selected and their percentage drug release was compared with that of marketed tablets.[17]

Preparation of Bilayer Tablets:
Bilayer tablets were prepared by taking best formulations from both the individual layers. Granules of Diclofenac Sodium blend were first introduced into the die cavity, a slight compression was made and then tramadol Hydrochloride blend was introduced into the die cavity followed by final compression with optimum hardness to form the bi layer tablets. Bilayer tablets were prepared and evaluated for various post compression parameters and in vitro dissolution.[18]

Evaluation of Bilayer Tablets:
All the post compression parameters like thickness, hardness, weight variation, friability, content uniformity of both the drugs were measured.[19-20]

Dissolution study:
In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 2 hr for Tramadol HCl IR and 12 hrs period for Diclofenac Sodium SR , using an automated paddle dissolution system. A minimum of 6 tablets per batch were tested. The media used was 0.1N HCl at a pH 2.0 and a volume of 750 ml for the first 2 hours after which 250 ml of 0.2 M sodium phosphate, tribasic, was added to give a final pH of 6.8 and maintained at 37+ 0.5◦C.

Test sample (5ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using UV (ultraviolet) spectrophotometer at λmax 271nm for Tramadol HCl and 276 nm for Diclofenac Sodium.

Table 1.formulation table containing Tramadol Hydrochloride immediate release layer

Sr no.	Ingredients (mg)	T1	T2	T3	T4	T5	T6	T7	T8	T9
1	Tramadol Hydrochloride	50	50	50	50	50	50	50	50	50
2	Sodium starch glycolate	3	6	7.5						
3	Cross povidone				3	6	7.5			
4	Cross carmellose sodium							3	6	7.5
5	Microcrystalline cellulose	95.5	92.5	91	95.5	92.5	91	95.5	92.5	91
6	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
7	Talc	1	1	1	1	1	1	1	1	1
8	PVP K-30	5% PVP IN IPA								

Table 2.formulation table containing diclofenac sodium sustain release layer

Sr. no.	Ingredients (mg)	D1	D2	D3	D4	D5	D6	D7	D8	D9
1	Diclofenac sodium	75	75	75	75	75	75	75	75	75
2	HPMC K4M	120	150	180						
3	HPMC K15 M				120	150	180			
4	HPMC K100 M							120	150	180
5	Micro crystalline cellulose	161	131	101	161	131	101	161	131	101
6	Magnesium sterate	2	2	2	2	2	2	2	2	2
7	Talc	2	2	2	2	2	2	2	2	2
8	PVP K-30	5% PVP IN IPA								

Table 3. Preformulation characters of Tramadol Hydrochloride and Diclofenac Sodium

Parameter	**Evaluation**	
API	TRAMADOL HYDROCHLORIDE	DICLOFENAC SODIUM
Description	Crystalline	Crystalline
Color	White	White
Odour	Odourless	Odourless
Bulk Density	0.338 gm/ml	0.56 gm/ml
True Density	0.423 gm/ml	0.64 gm/ml
Carr's Index	20.09%	14.28%
Hausner's Ratio	1.15	1.14
Melting Point	STD : 180 ^{0}C OBS : 178-184 ^{0}C	STD : 284^{0}C OBS : 283-285 ^{0}C
Solubility	0.1 N HCl:20.4±0.003	0.1N HCl:0.0012±0.002 pH 6.8 phosphate buffer:1.36±0.01

Assay: Tramadol hydrochloride
Table 4. Assay (%purity)

Time(Months)	**Physical**		**Chemical**
	Colour	**Odour**	**Assay**
0	White crystalline powder	Odourless	101.59%
3	White crystalline powder	Odourless	99.93%
6	White crystalline powder	Odourless	96.60%

Assay: Diclofenac sodium
Table 5.Assay (%purity)

Time(Months)	**Physical**		**Chemical**
	Colour	**Odour**	**Assay**
0	White to off white crystalline powder	Odourless	102.50%
3	White to off white crystalline powder	Odourless	100.37%
6	White to off white crystalline powder	Odourless	99.67%

From the experimental results, it was observed that there was no significant change in the % purity of API until 6 months under recommended stability condition at 40°C±2℃ and 75%±5 RH. Hence, it was concluded that API is stable.

Table 6.Calibration curve of Tramadol hydrochloride in pH 1.2 buffer

Conc.(µg/ml)	Abs(λmax 271nm)
0	0.000
20	0.186
40	0.287
60	0.398
80	0.535
100	0.637

Figure 1.Calibration curve of Tramadol hydrochloride in pH 1.2 buffer

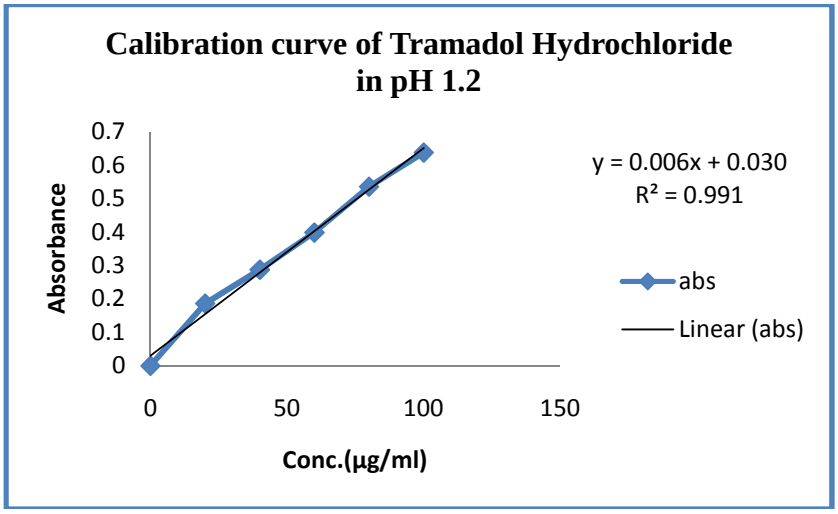


Table 7.Calibration curve of Diclofenac Sodium in pH 6.8 buffer

Conc. (µg/ml)	Abs(λmax-276nm)
0	0.000
2	0.075
4	0.113
6	0.171
8	0.243
10	0.317
12	0.339
14	0.4
16	0.461
18	0.518
20	0.593

Figure 2.Calibration curve of Diclofenac Sodium in pH 6.8 buffer

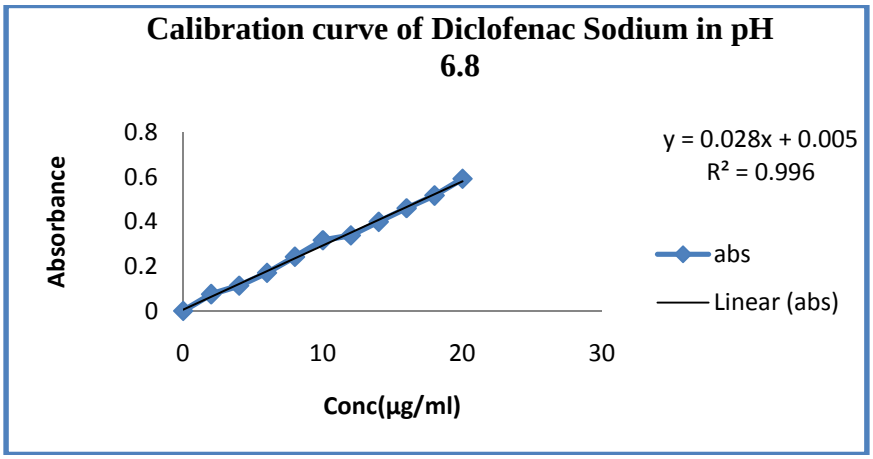
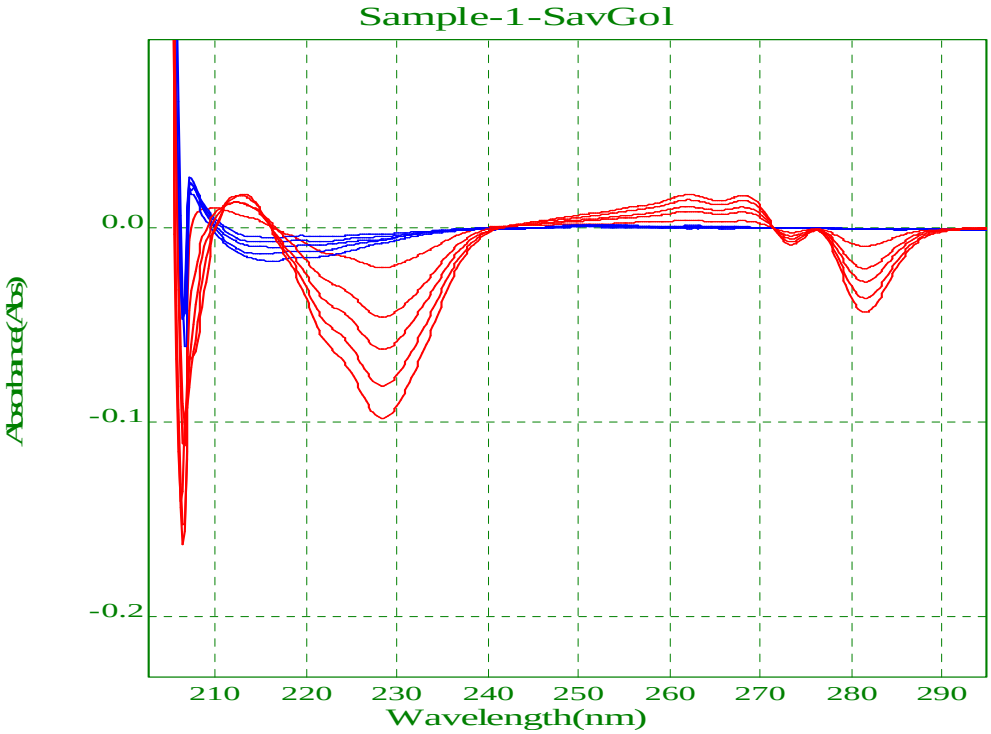


Figure.3 Development of First Order Derivative Spectrophotometric of Tramadol Hydrochloride and Diclofenac Sodium



First order derivative spectroscopy of tramadol hydrochloride and diclofenac sodium:
Quantitative analysis for simultaneous determination of TRA and DIC in combined dosage form.9-45 µg/ml concentration of diclofenac sodium and 6-30µg/ml concentration of tramadol hydrochloride was prepared in 1.2 pH buffer. The overlain first derivative spectrums of TRA and DIC at different concentration were recorded. At the zerocrossing of diclofenac sodium at 280nm tramadol showing linear absorption. Diclofenac sowing zero absorbance at all the λmax so no interference was found in tramadol hydrochloride and diclofenac sodium in combined dosage form.

Figure.4 FTIR Spectroscopy: Diclofenac sodium

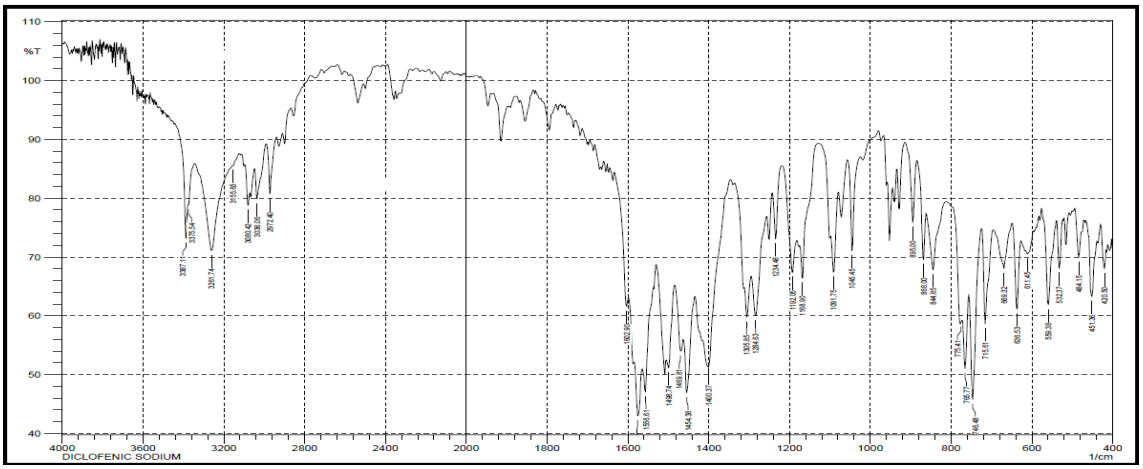


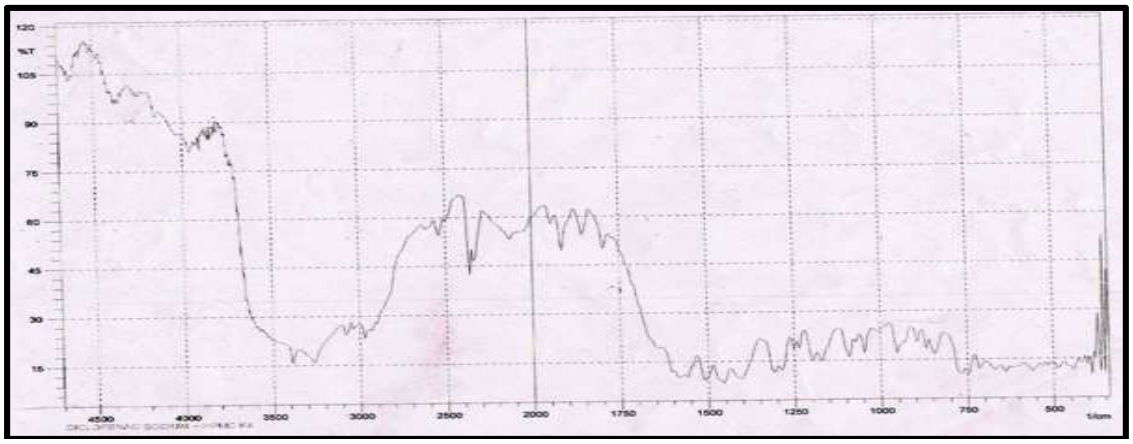
Table-8 Characteristic peaks of Diclofenac sodium

IR Spectrum	Standard peaks value cm-1	Observed peaks value cm-1	Groups	Stretching/ deformation
DICLOFENC SODIUM	1600-1475	1556.61, 1498.74	C=C(aromatic)	Stretching
	1320-1210	1305.85	C-O Stretching	Stretching
	1556	1556.61	Dichlorophenyl ring	Stretching
	1300-1000	1284.63	C-CO-C Stretching	Stretching

Table 9.Characteristic peaks of Tramadol hydrochloride

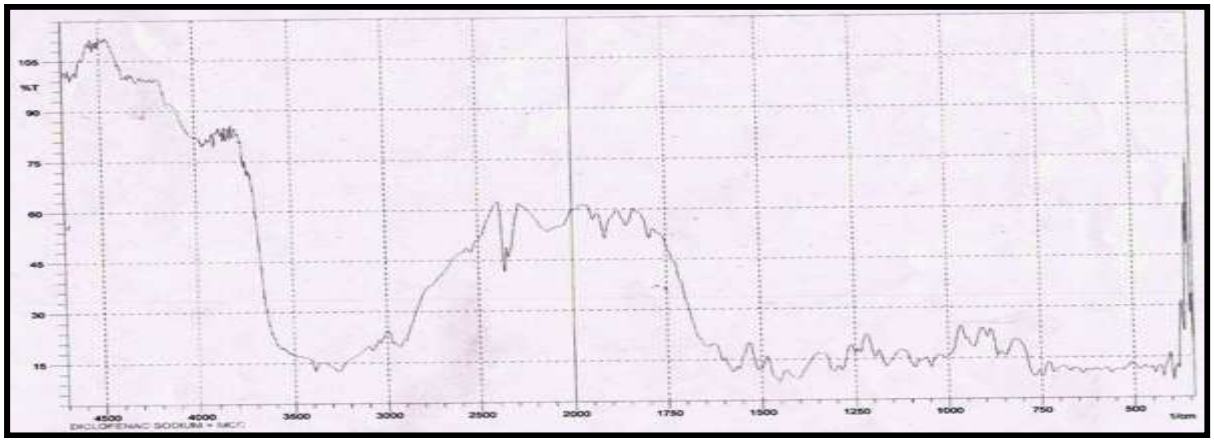
IR Spectrum	Standard Peaks value cm-1	Observed peaks value cm-1	Groups	Stretching/ Deformation
Tramadol Hydrochloride	3150-3050	3136.36	C-H stretching (aromatic)	Stretching
	3000-2850	3417.98	C-H stretching (aliphatic)	Stretching
	3500-3100	3343	N-H stretching	Stretching
	1350-1000	1219.05	C-N stretching	Stretching
	1600-1475	1411.96	C=C stretching	Stretching
	1300-1000	1219.05,1161.19	C-O stretching	Stretching

Figure.5 FTIR of Diclofenac sodium + HPMC K4M



Characteristic peaks of drug in mixture were obtained at1245, 1176, 1478, 2986 that shows no significant change in original peaks position. Hence no interaction between Drug and excipient was considered.

Figure 6. FTIR of Diclofenac sodium + Microcrystalline cellulose:



Characteristic peaks of drug in mixture were obtained at 1176, 1218, 1556,1247,1411,1454, 2956 that shows no significant change in original peaks position. Hence no interaction between Drug and excipient was considered.

Figure 7.FTIR Spectroscopy: Tramadol hydrochloride

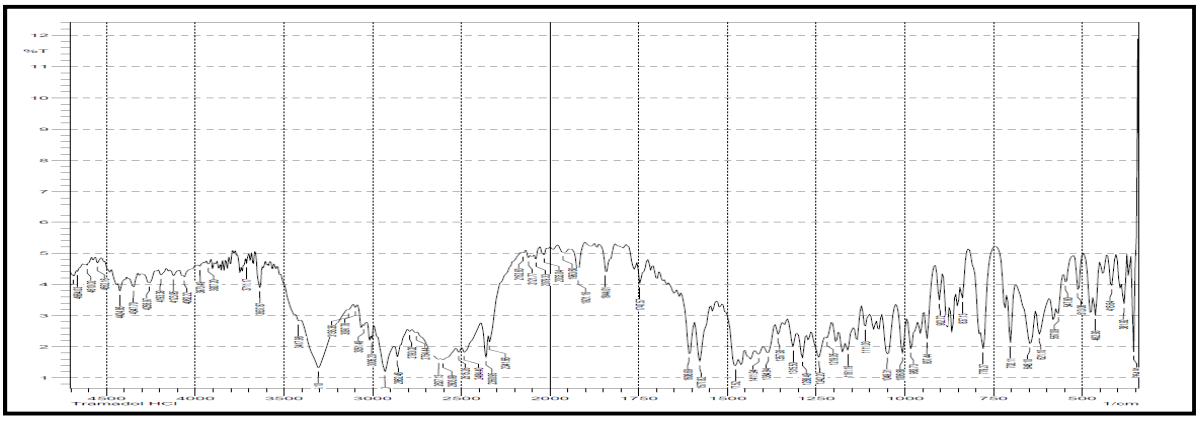
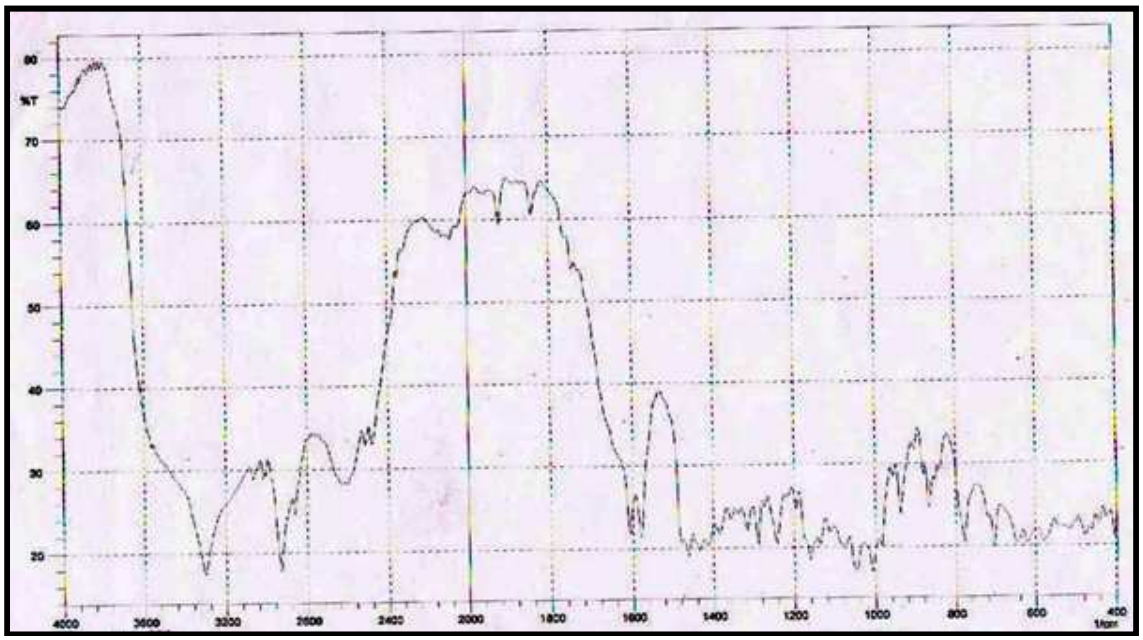
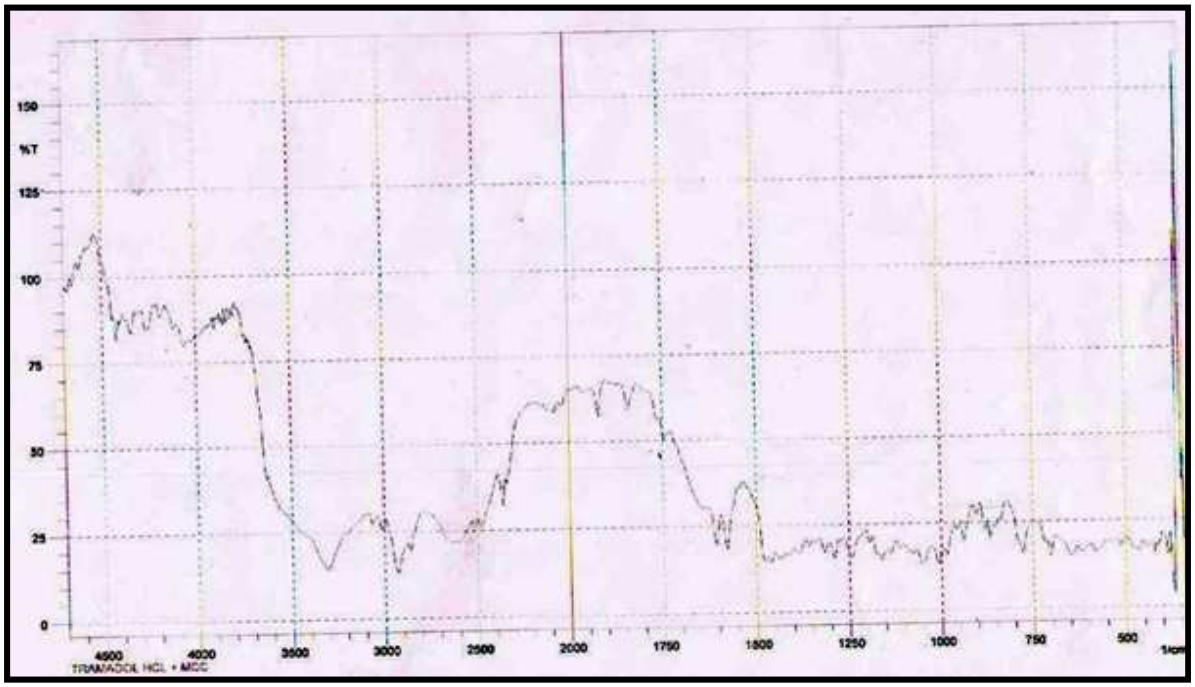


Figure 8.FTIR of Tramadol hydrochloride + sodium starch glycolate



Characteristic peaks of drug in mixture were obtained at 925, 1219, 1350, 1610, 3275.That shows no significant change in original peaks position. Hence no interaction between Drug and excipient was considered

Figure 9.FTIR of Tramadol hydrochloride+microcrystalline cellulose



Characteristic peaks of drug in mixture were obtained at 1249, 1411, 1454, 3417,.That shows no significant change in original peaks position. Hence no interaction between Drug and excipient was considered

Table.10 Result of Precompression perameters of Tramadol hydrochloride

Formulation Code	Angle of Repose (θ) (±SD)	Bulk Density gm/cm^{-3} (±SD)	Tapped Density gm/cm^{-3} (±SD)	Carr's Index (%)(±SD)	Hausner ratio (±SD)
T1	27.44±0.15	0.387±0.08	0.472±0.02	17.89±0.34	1.2196±0.08
T2	29.74±0.12	0.343±0.10	0.427±0.04	19.67±0.62	1.2448±0.05
T3	29.23±0.08	0.380±0.06	0.465±0.08	18.27±0.78	1.2236±0.07
T4	25.28±0.16	0.384±0.13	0.47±0.03	18.29±0.76	1.2239±0.08
T5	27.59±0.21	0.356±0.15	0.438±0.04	18.72±0.53	1.2303±0.05
T6	27.74±0.45	0.376±0.09	0.457±0.08	17.72±0.42	1.2154±0.04
T7	29.43±0.23	0.362±0.04	0.446±0.06	18.83±0.20	1.2320±0.06
T8	26.53±0.09	0.361±0.09	0.443±0.07	18.28±0.90	1.2237±0.05
T9	26.39±0.07	0.374±0.03	0.454±0.05	17.62±0.58	1.2139±0.05
(n=3, ± S.D) (S.D= Standard deviation)					

All the batches were evaluated for the pre-formulation studies. The flow property was Excellent and good for all the batches.Results shown that values of % compressibility was found between17.62 to 18.83 indicating that having % compressibility is good to fair. Also the values of Hausner's ratio are ranging from 1.21 to 1.23. Results of the hausner's Ratio revealed that the all the formulation having good flow property.

Table 11. Result of Precompression perameters of Diclofenac sodium

Formulation Code	Angle of Repose (θ) (±SD)	Bulk Density gm/cm^{-3} (±SD)	Tapped Density gm/cm^{-3} (±SD)	Carr's Index (%) (±SD)	Hausner ratio (±SD)
D1	21.62±0.09	0.542±0.06	0.634±0.04	14.51±0.86	1.1697±0.05
D2	20.85±0.10	0.530±0.08	0.626±0.07	15.33±0.25	1.1811±0.07
D3	21.75±0.13	0.528±0.12	0.617±0.09	14.42±0.53	1.1685±0.05
D4	21.83±0.15	0.543±0.08	0.638±0.08	14.89±0.27	1.1749±0.09
D5	22.97±0.08	0.535±0.09	0.629±0.07	14.94±0.68	1.1757±0.07
D6	20.68±0.09	0.500±0.09	0.598±0.06	16.38±0.41	1.186±0.06
D7	21.33±0.08	0.549±0.07	0.644±0.06	14.75±0.55	1.1730±0.07
D8	22.97±0.12	0.539±0.14	0.635±0.05	15.11±0.72	1.1781±0.06
D9	22.33±0.16	0.527±0.15	0.623±0.09	15.40±0.69	1.1821±0.06
(n=3, ± S.D) (S.D= Standard deviation)					

All the batches were evaluated for the pre-formulation studies. The flow property was Excellent and good for all the batches.Results shown that values of % compressibility were found between14.42 to 15.40 indicating that having % compressibility is good. Also the values of Hausner's ratio are ranging from 1.16 to 1.18. Results of the hausner's Ratio reveals that the all the formulation having good flow property.

Table 12. Result of Post compression parameter of Tramadol Hydrochloride

Formulation code	Hardness(kg/cm^2)	Thikness(mm)	%friability	weight variation	Disintegration time(sec)
T1	3.2±0.3	1.6±0.11	0.58	Pass	79±1.95
T2	3.2±0.3	1.6±0.1	0.48	Pass	55±1.76
T3	3.4±0.4	1.7±0.05	0.46	Pass	52±2.11
T4	3.4±0.3	1.6±0.1	0.45	Pass	95±2.85
T5	3.6±0.2	1.6±0.1	0.48	Pass	73±1.02
T6	3.2±0.2	1.7±0.05	0.55	Pass	59 ±2.35
T7	3.2±0.2	1.6±0.1	0.57	Pass	92±1.34
T8	3.4±0.3	1.7±0.05	0.49	Pass	65±1.12
T9	3.4±0.3	1.7±0.05	0.45	Pass	56±1.01
(n=3, ± S.D) (S.D= Standard deviation)					

Table.13 Result of Post compression parameter of Diclofenac sodium

Formulation Code	Hardness Kg/cm^2	Thickness mm	% Friability	Weight variation
D1	4.2±0.2	2.6±0.05	0.81	Pass
D2	4.4±0.4	2.7±0.1	0.77	Pass
D3	4.6±0.8	2.6±0.1	0.85	Pass
D4	4.6±0.2	2.8±0.1	0.79	Pass
D5	4.2±0.2	2.8±0.05	0.79	Pass
D6	4.4±0.4	2.6±0.05	0.84	Pass
D7	4.2±0.2	2.8±0.1	0.72	Pass
D8	4.8±0.4	2.7±0.1	0.81	Pass
D9	4.6±0.1	2.8±0.1	0.87	Pass
D8	4.6±0.2	2.8±0.1	0.76	Pass
D9	4.4±0.2	2.6±0.05	0.73	Pass
Here SD =Standard Deviation And n=3 Runs				

Table 14. % Drug release of the Tramadol hydrochloride

Time (min)	% Drug released(Mean±S.D)								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
5	35.50 ± 1.32	37.67± 1.77	38.29± 3.12	37.05± 2.34	38.91± 1.59	40.46± 1.39	33.64± 1.54	34.57± 1.34	36.74± 1.45
10	68.71 ± 2.5	70.57± 2.89	72.12± 2.1	64.36± 2.59	63.43± 2.36	68.08± 2.1	67.77± 2.9	68.71± 1.59	70.26± 1.52
15	85.15 ± 1.90	87.02± 2.74	88.26± 2.5	77.08± 1.82	78.64± 2.60	84.84± 1.45	79.88± 2.6	83.29± 2.3	85.46± 2.31
30	90.74 ± 2.34	95.4± 1.29	99.43± 3.25	90.12± 3.5	85.77± 2.23	97.57± 1.42	91.67± 1.29	92.41± 3.1	94.77± 3.6
45	94.77 ± 2.3	97.57± 2.54	-	94.77± 2.18	97.88± 3.28	99.24± 2.65	95.08± 1.77	96.02± 2.99	96.95± 2.1
60	-	-	-	98.81± 1.6	-	-	99.43±	-	-

Table 15. % Drug release of the Diclofenac sodium

Time (hr)	% Drug released(Mean±S.D)								
	D1	D2	D3	D4	D5	D6	D7	D8	D9
1	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-
3	15.42± 1.2	13.24± 3.22	7.37± 1.16	14.83± 1.4	10.85± 3.64	6.16± 2.45	12.07± 0.95	9.19± 1.4	6.57± 1.62
4	25.83± 2.4	22.54± 1.87	15.33± 1.1	24.39± 2.9	19.02± 1.4	14.78 ±1.63	25.35± 1.6	19.41± 1.25	15.12± 1.34
5	39.22± 3.2	30.75± 2.43	24.01± 0.92	35.34± 3.15	26.95± 2.4	19.69 ±2.57	34.88± 2.5	26.67± 1.39	22.54± 3.12
6	51.90± 1.7	43.43± 1.67	33.03± 1.6	43.52± 1.84	32.70± 3.26	25.40 ±2.80	46.42± 1.3	35.27± 2.87	28.21± 1.74
7	63.73± 1.3	56.74± 2.98	40.88± 1.30	52.42± 1.2	41.21± 1.34	32.57 ±3.42	54.60± 2.31	44.76± 2.8	38.15± 1.52
8	70.78± 1.67	67.31± 3.10	54.11± 2.1	65.42± 2.31	49.35± 2.48	42.18 ±2.3	61.14± 1.30	56.51± 2.4	45.28± 2.89
9	81.52± 2.98	72.20± 1.87	62.19± 1.4	72.47± 3.21	56.78± 2.21	49.69 ±1.69	67.25± 2.50	59.54± 3.68	51.41± 3.2
10	91.25± 3.22	80.77± 2.43	67.27± 1.85	78.01± 1.43	68.82± 1.6	60.10 ±2.44	75.96± 2.61	64.48± 2.64	57.96± 2.5
11	99.85	93.73± 3.21	75.63± 2.65	92.12± 1.72	81.38± 2.35	69.37 ±1.53	85.62± 1.9	71.62± 3.18	61.02± 2.38
12	-	99.18± 1.67	81.88± 1.34	102.9± 3.4	87.86± 1.63	76.08 ±1.77	94.57± 1.33	79.17± 3.78	71.30± 1.80

Figure 10 In Vitro drug release profile of diclofenac sodium formulation (D1-D3) in pH 6.8 buffer

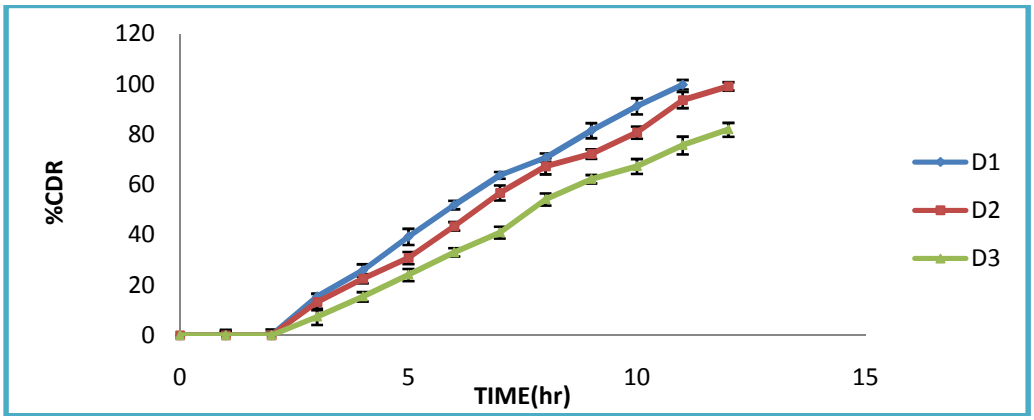


Figure 11 In Vitro drug release profile of diclofenac sodium formulation (D4-D6) in pH 6.8 buffer

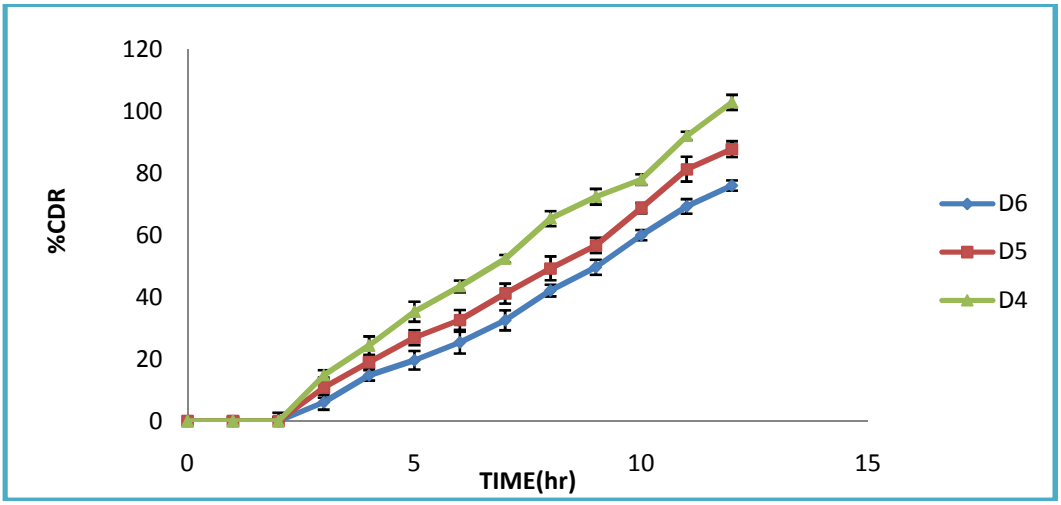


Figure.12 In Vitro drug release profile of diclofenac sodium formulation (D7-D9) in pH 6.8 buffer

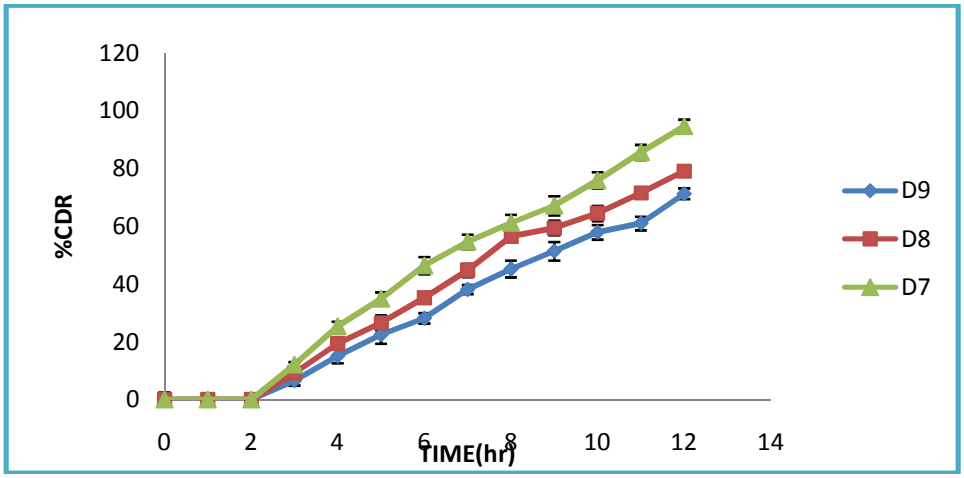


Figure.13 In Vitro Drug Release Profile of Tramadol hydrochloride formulation (T1-T3) in pH 1.2 Buffer

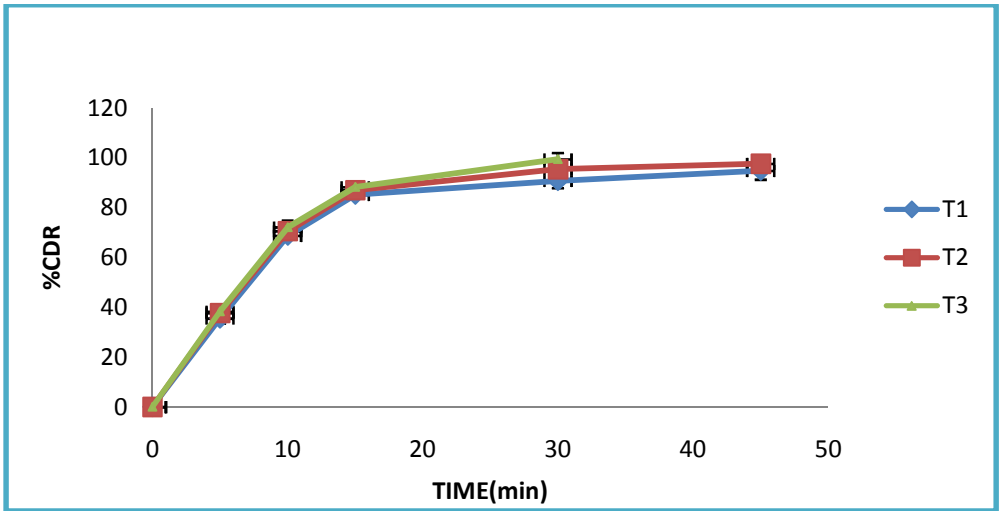


Figure.14. In Vitro Drug Release Profile of Tramadol hydrochloride formulation(T4-T6) in pH 1.2 Buffer

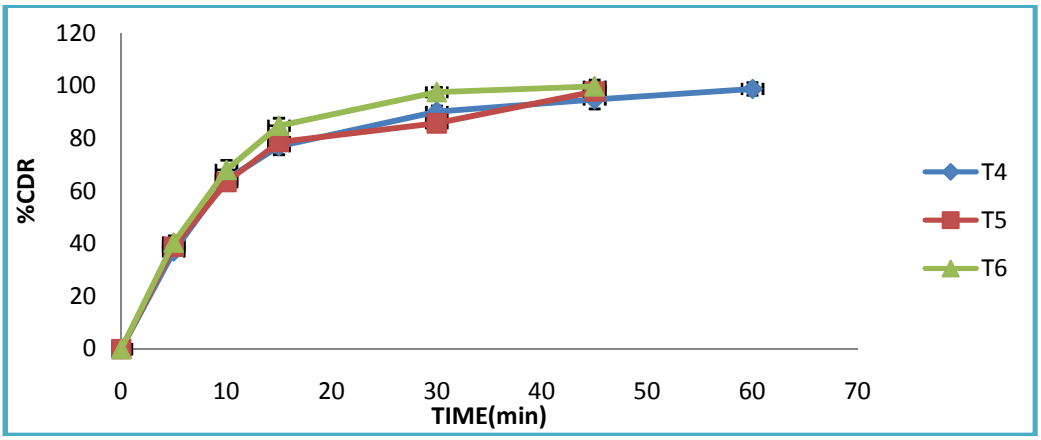


Figure.15 In Vitro Drug Release Profile of Tramadol hydrochloride formulation (T7-T9) in pH 1.2 Buffer

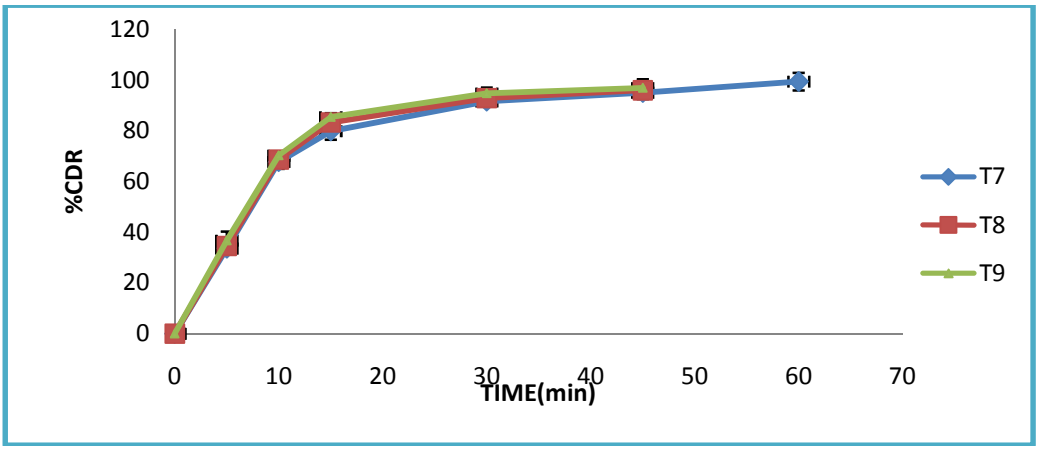


Table 16.Formulation Table for Optimized Bilayered Tablet

Sr no.	Ingredients (Immediate release layer)	Quantity(mg)	Ingredients (Sustain release layer)	Quantity (mg)
1.	Tramadol hydrochloride	50	Diclofenac sodium	75
2.	Sodium starch glycolate	7.5	HPMC K4M	150
3.	Micro crystalline cellulose	91	Micro crystalline cellulose	131
4.	Magnesium stearate	0.5%	Magnesium stearate	2%
5.	Talc	1%	Talc	2%
6.	PVP K-30	5% PVP IN IPA		

Table 17.Post compression parameter of optimized bilayer tablet

Formulation Code	F1
Weight Variation	Pass
Hardness (Kg/cm^2)	6.4±0.4
Thickness (mm)	4.4 ±0.1
Friability	Pass
Weight variation	Pass
Disintegration time of tramadol hydrochloride (sec)	54±1.2
SD : Standard Deviation, n=3	

Table18.In Vitro drug release profile of bilayer tablet containing tramadol Hydrochloride and diclofenac sodium.

Time(min)	%Drug Release	
	T3	D2
0		
5	36.2±1.89	-
10	72.85±1.34	-
15	88.26±0.98	-
30	99.18±1.32	-
180	-	12.55±2.12
240	-	23.13±0.98
300	-	32.75±3.22
360	-	43.65±1.87
420	-	55.6±2.43
480	-	63.31±1.67
540	-	74.4±2.98
600	-	80.75±3.22
660	-	90.09±1.87
720	-	98.24±1.20

Figure 16.In Vitro drug release profile of bilayer tablet containing tramadol hydrochloride and diclofenac sodium

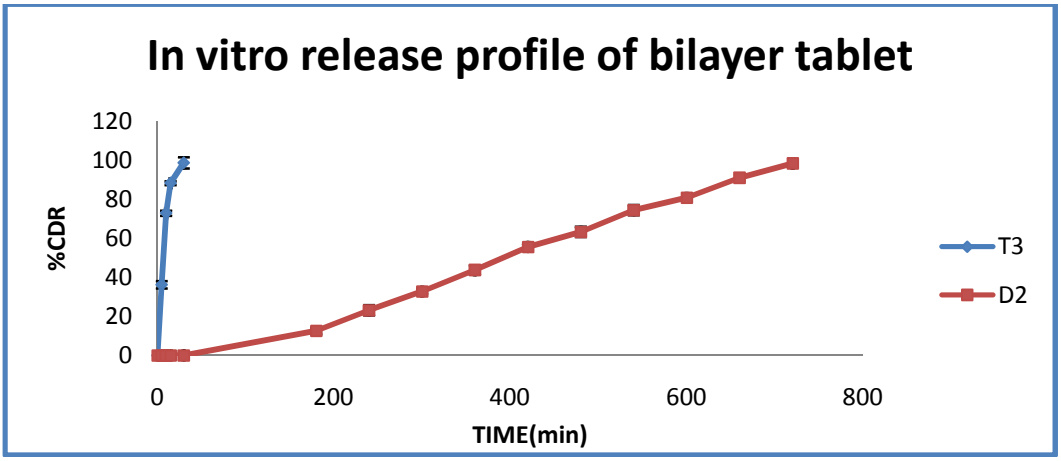


Table 19.Stability Study of dosage form

Specification	0 month	1 month	2month
In vitro release profile			
Tramadol hydrochloride	99.18±1.32 in 30 minute	98.85±1.4 in 30 minute	97.64±2.3 in 35 minute
Diclofenac sodium	98.24±1.2 in 12 hr	97.5±1.6 in 12 hr	96.76±1.28 in 12hr
Disintegration time(sec)			
Tramadol hydrochloride	54±1.2	55±1.7	56±1.12
Assay (%content uniformity)			
Tramadol hydrochloride	98.52%	98.4%	98.02%
Diclofenac sodium	99.75%	99.33%	98.54%

Results and Discussion

Optimization of bilayer tablet.

Attempt was made to formulate combination of bi layer tablet containing tramadol hydrochloride immediate release layer and diclofenac sodium sustain release layer. FT - IR studies reveal that there were no significant interactions between both the drugs and between the drugs and their respective excipients. For achieving sustained release of diclofenac sodium three hydrophilic swellable polymers like HPMC K4M, HPMC K15M, and HPMC K100M were used. For achieving immediate release of tramadol hydrochloride three super disintegrating agent were used.

Optimization of immediate release layer of tramadol hydrochloride.

From the results it was concluded that disintegration activity decreases in the order of Cross Povidone < Crosscarmellose Sodium < Sodium Starch Glycolate. As Crospovidone concentration increases from (2-5%) disintegration time decreases gradually. Similarly from T7 – T9 as the concentration of Croscarmellose Sodium increases from (2-5%) disintegration time decreases proportionally.

In formulations T1 – T3, Sodium Starch Glycolate was used as the superdisintegrants,as the concentration increases from (2-5%) disintegration time decreases. Amongst the three superdisintegrants were used SSG was the better disintegrant showing lesser Disintegration time around 54±1.2
Thus T3 releasing 99.18 % after 30 min was selected as best formulation release of tramadol hydrochloride.

Optimization of sustain release layer of Diclofenac sodium.
From the graph it was concluded that release retardation capacity increase in order of HPMC K100M>HPMC K15M>HPMC K4M due to the higher viscosity grade and swelling behavior of polymer matrix.
In formulation,from D1-D3 as HPMC K4M concentration increase release was decrease. In formulation D4-D6 as concentration of HPMC K15 M increase release was more retarded then comparable to HPMC K4M.
In formulation D7 to D9 high viscosity grade was taken amongst the three viscosity garde.i.e HPMC K100M, as concentration of polymer increase release was more retarded then comparable to both the grade that is HPMC K4M and HPMC K15M. Formulation D2 was optimized on the basis of *in vitro* sustained drug release for 12 hr, i.e 98.24 %. D2 formulation fulfills their official requirement of 80% drug release within 8th hour in simulated intestinal medium.

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