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Research Article

**DEVELOPMENT AND EVALUATION OF TAPENTADOL
HYDROCHLORIDE EXTENDED RELEASE TABLET****K. Ramanji Reddy¹, Dr. S. Jaya², V. Sandhya Rani², Dr. Chandaka Madhu¹**¹Scientist, Startech Labs Pvt. Ltd., Madinaguda, Hyderabad, TS-5000050²Anurag Pharmacy College, Ananthagiri (V), Kodad (M), Nalgonda, TS-508206**Abstract:**

Extended release tablets of Tapentadol hydrochloride were prepared by wet granulation method using microcrystalline cellulose PH101, sodium carboxy methyl cellulose, polyvinyl pyrrolidone (K-90), methocel K 200M and plasdone. The drug and excipients compatibility was studied by FT-IR which showed no physico-chemical interaction. The polymer used Hydroxy propyl ethyl cellulose was granular blend. Also it was concluded that it improves the drug release at 12th hour. The kinetic treatment of the drug release data of the prepared formulations followed zero order drug release the prepared formulations followed Higuchi profile. It indicated that the drug release from the tablets involves anomalous diffusion mechanism or diffusion coupled with erosion, and directly proportional to square root of time as indicated by the n value of 0.66 in Korsmeyer's plot. On comparing equation of straight line and regression coefficient (R²) with Innovator, formulation F8 shows similarity of results with innovator. Hence F8 was considered as formulation with extended release profile as indicated by 95.2% of drug released at the end of 12hrs. The stability studies were carried out for a period of 3 months as per ICH guidelines. There were no significant changes in dissolution profile and other parameters of the optimized formulation F8. To conclude, formulation F8 containing higher concentration of polymer (HPMC) and optimum concentration of super disintegrant showed drug release of 95.2% at the end of 12h, and this optimized formulation can be selected for further studies.

Key words: Tapentadol hydrochloride , microcrystalline cellulose , Extended release tablets, stability**Corresponding author:****K. Ramanji Reddy, M.Sc, M.Phil., (Ph.D).**

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INTRODUCTION:

Chronic pain is defined by the “International Association for study of pain” as pain that persists beyond normal tissue healing time. A recent market research report indicates that more than 1.5 billion people worldwide suffer from chronic pain and that approximately 3–4.5% of the global population suffers from neuropathic pain [1].

Opioid analgesics such as Morphine sulfate, Oxycodone, Oxymorphone, Hydromorphone, Tramadol, and Tapentadol are increasingly prescribed for the treatment of painful chronic conditions. Despite their established place in pain management, traditional μ -opioid receptor agonists are prescribed only for extreme pain as they are associated with gastrointestinal (GI) and other dose-limiting adverse events [2]. These factors can compromise the adequacy and quality of pain management and lead to treatment discontinuation.

Tapentadol hydrochloride (TAP) is the newer drug of the centrally acting analgesic class approved by USFDA in 2008, after more than 25 years from the last approved opioid analgesic Tramadol. Its potency is between the highly potent morphine and the comparatively less-potent tramadol. It has two complementary mechanisms of action within a single molecule, binding weakly to the μ -opioid receptor site and inhibiting the reuptake of norepinephrine. Its unique dual mechanism of action makes it an agent with automatic multimodal benefit [3].

Conventional drug delivery systems have little control over the drug release and so effective concentration at the target site cannot be achieved and this kind of dosing pattern may result in unpredictable plasma concentrations. Oral controlled drug delivery dosage forms provide desired drug release pattern for longer periods of time and so the rate and extent of drug absorption from oral controlled drug delivery formulations can be predicted. Various approaches used for achieving controlled release of the drug includes, use of dissolution-controlled release systems, diffusion-controlled release systems, dissolution and diffusion-controlled release systems, ion exchange resins drug complexes, slow dissolving salts and complexes, pH dependent formulations, and Hydrodynamic controlled systems etc. Drug release from these formulations may be affected by pH, GI motility, and presence of food in the GI tract. However, drug release from osmotic drug delivery system is not affected by physiological factors [4]. Osmotically controlled systems utilize osmotic pressure for controlled delivery of the drug. Amongst the

controlled release devices, osmotic systems hold a stable place because of its reliability to deliver the API at predetermined zero-order rate for prolonged period of time making them standard dosage forms for the constant delivery of contents. Main scope of formulating Tapentadol as extended release is to reduce the administration intervals. Moreover, high plasma peak levels which go along with side effects can be optimized. Extended release formulations are important for long-term treatment. By reducing the frequency of dose, safety and efficacy of the drug can be improved by which patient compliance can be increased and drug plasma levels are controlled. The present work is to design and evaluate Tapentadol Hydrochloride tablets by wet granulation method using different hydrophilic polymers

METHOD AND METHODOLOGY:

Materials required:

Chemicals:

Tapentadol-hcl, microcrystalline cellulose, pvpk-30, hpmck-100, ac-di-sol, providone, sylloid.

Instruments:

Balance, sieves, tapped density tester, mixer granulator, mechanical stirrer, dryer, compression machine, vernier calipers, hardness tester, disintegration apparatus, stability chambers, phmeter and dissolution

Preformulation studies [5]

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objectives of preformulation studies are to develop a portfolio of information about the drug substance, so that these information's are useful to develop the formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. Following are the test performed for the preformulation study.

Organoleptic Characteristics:

The color, odour, and taste of the drug were characterized and recorded using descriptive terminology.

Drug-excipients compatibility studies

The proper design and the formulation of a dosage form require consideration of the physical, chemical and biological characteristics of the drug and excipients used in fabricating the product. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, easy to administer and safe.

The compatibility studies provide the framework for the drugs combination with excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets.

Compatibility studies were carried out by Fourier Transformed-Infra Red and Differential Scanning Calorimeter. In this study the pure drug spectra and drug and physical mixer of excipients spectra were compared.

Procedure:

Weighed amount of drug (1mg) was mixed with 99mg of potassium bromide and dried at 40-50°C. The mixture was taken and compressed under 7 ton pressure in a hydraulic pressure to form a transparent pellet. The pellet was scanned in IR spectrophotometer.

Angle of repose [6]:

The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose.

Method:

The blend was passed through a funnel fixed to a burette stand at a height of 4 cm. A graph paper was placed below the funnel on the table. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula:

$$\text{Angle of repose } (\theta) = \tan^{-1} (h/r)$$

Where,

h = Height of the pile
r = Radius of the pile

Bulk density [6]:

The bulk density is used as a measure to describe packing materials or granules.

Method:

Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately weighed amount (25 g) of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

$$\text{Bulk density} = W/V_0 \text{ g/m}$$

Where, W = Mass of the blend,
V₀ = Untapped volume

Tapped density [6]:**Method**

It was measured by transferring a known quantity (25 gms) of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 500, 750 and 1250 taps. The tapped density was determined as the ratio of mass of the blend to the tapped volume.

$$\text{Tapped density} = W/V_f \text{ g/ml}$$

Where, W = Mass of the blend,
V_f = tapped volume.

Compressibility index [6]:

It is measured by tapped density apparatus for 500, 750 and 1250 taps for which the difference should be not more than 2 %. Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

$$\text{Compressibility index} = [(V_0 - V_f)/V_0] \times 100$$

(or)

Percentage compressibility = [(Tapped density – Bulk density)/Tapped density] X 100

Hausner's ratio [6]:

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

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

Table 1: Flow properties with respect to Angle of repose, Compressibility index and Hausner's ratio

S. No	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner's ratio
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	> 66	>38	>1.6

Loss on drying [7]

The Loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. The loss on drying of the blend (2 g) was determined by using electronic LOD apparatus at 105°C.

Formulation Development of Tapentadol Hydrochloride Tablets**Table 2: Composition of Tapentadol Hydrochloride Extended Release Tablets (mg)**

S.no	Composition	F1 Qty/mg	F2 Qty/mg	F3 Qty/mg	F4 Qty/mg	F5 Qty/mg	F6 Qty/mg	F7 Qty/mg	F8 Qty/mg
1	Tapentadol hydrochloride	291.20	291.20	291.20	291.20	291.20	291.20	291.20	291.20
2	Microcrystalline cellulose pH101	98.80	98.80	98.80	98.80	98.80	98.80	98.80	98.80
3	Polyvinyl pyrrolidone K 30	15	15	15	15	15	15	15	15
4	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
5	HPMC K 100 M	80	-	85	90	95	98	100	100
6	Croscarmellose sodium	64	-	54	46.75	36.75	34	34	32
7	PlasdoneS630	30.75	-	35.75	38.00	43.00	42.75	40.75	42.75
8	Colloidal silicon dioxide	13.50	13.50	13.50	13.50	13.50	13.50	13.50	13.50
9	Magnesium stearate	6.75	6.75	6.75	6.75	6.75	6.75	6.75	6.75
10	MCC pH102	-	44.0	-	-	-	-	-	-
11	Xanthan Gum	-	90.0	-	-	-	-	-	-
12	Hydroxy propyl cellulose LF	-	40.75	-	-	-	-	-	-

Wet granulation method [8]**Procedure for wet granulation (F1 TO F8):**

API, MCC PH 101, croscarmellose sodium, methocel K200M were weighed and mixed for 2 min. The above mixture was passed through sieve # 40. Povidone K30 was dispersed in sufficient quantity

of purified water by stirring. Then the above mixture was granulated using binder solution in rapid mixer granulator. The wet mass was passed through sieve #12. The sieved mixture was dried using FBD and the temperature was maintained at 60°C until the moisture content in the blend comes to 2.0 to 3.5

%.The dried blend was passed through sieve # 20 and then pre lubricated using Aerosil for 20 min and then lubricated with magnesium stearate in blender for 5 min.Then finally the lubricated blend was compressed using 9.5 mm round shape standard concave punch.

Procedure for Film Coating:

The coating solution was prepared by dispersing Opadry Blue II in water. The tablets were then charged into the pan of coating machine (Ideal cures). The coating solution was sprayed over the tablets using 1.5mm air nozzle with an atomizing air pressure of 3-4 atm.The pan speed was maintained at 30 RPM. The inlet and outlet temperature were maintained at 60°C and 55°C respectively. The coating was performed until required weight gain was obtained.

Evaluation parameters of tablets

Physical appearance [9]:

The tablets were inspected for smoothness, absence of cracks, chips and other undesirable characteristics. If they are colored, it includes examination for mottling and other evidence of uneven color distribution except where they are used intentionally. If they are coated tablets the coating problems like picking and sticking, bridging, capping, erosion, twinning, chipping and orange peel.

Weight variation test [10]:

Twenty tablets were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight

Hardness [11]:

The hardness test is performed to measure the tablet strength. Tablet should be hard enough to withstand packing and shipping. Electro lab hardness tester was used for the determination of hardness of tablets. The hardness of 10 tablets was noted and the average hardness was calculated. It is expressed in kp or kg/cm².

Thickness [12]:

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm. The thickness of the tablet is mostly related to the tablet hardness and can be used as an initial control parameter.

Percentage friability [12]:

The friability test gives an indication of tablets ability to resist chipping and abrasion on handling during packaging and shipping. Usually for conventional tablets friability value of 1.0% or less is desirable. If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. The tablets were rotated in the Roche friabilator for 100 revolutions at 25 rpm and then de-dusted and reweighed.

The tablets that loose less than 1% weight were considered to be compliant.

The percentage friability is expressed as the loss of weight and is calculated by the formula:

$$\text{Percentage friability} = ((A-B)/B) \times 100$$

Where,

A = Initial weight of tablets

B = Final weight of tablets after 100 revolutions

Assay [13,14]: Assay of Tapentadol hydrochloride tablet was carried out by the HPLC method by the following procedure.

a) Chromatographic conditions:

Column : Zodiac C₁₈250×4.6 mm, 5μ or equivalent.
 Detector : Wavelength at 279 nm.
 Flow rate : 0.7ML/min
 Injection volume : 10μL
 Run time : 15min
 Diluent : Mobile phase
 Mobile phase : Buffer: Acetonitrile (65:35v/v)
 Elution : Isocratic

b) Buffer preparation:

One mL of Trifluoro acetic acid was transferred into 1000mL of Milli-Q water, and its pH was adjusted to 2.50±0.05 with triethyl amine, then the solution was filtered through 0.45 micron filter, and it was sonicated to degas the buffer.

c) Standard preparation:

Tapentadol hydrochloride standard equivalent to 25mg of tapentadol was weighed accurately and transferred into 25 ML volumetric flask and 10mL of methanol was added, then it is sonicated for 5 minutes to dissolve and finally volume was adjusted with diluent. Further 5mL of this solution was diluted to 25mL with diluent.

d) Sample preparation:

Ten tablets were crushed to powder and the sample powder was weighed equivalent to 100mg of tapentadol and transferred into 50mL volumetric flask and 30mL of methanol was

added, then sonicated for 15 min to dissolve and further volume was adjusted with methanol. Further 5mL was diluted to 50 mL with diluent.

e) System suitability requirements for standard:

- a) Tailing factor : NMT 2.0
 b) Theoretical plates : NMT 3000
 c) %RSD : NMT 2.0

f) Procedure: About 10 μ L of diluent was injected as blank, standard solution five times for system suitability criteria, then inject two times of sample preparation. Calculate the % of tapentadol by the given formula.

Calculation:

$$\% \text{ of Assay} = \frac{\text{Sample area}}{\text{Avg. std. area}} \times \frac{\text{Std. wt.}}{25} \times \frac{5}{25} \times \frac{50}{\text{spl. wt}} \times \frac{50}{5} \times \frac{\text{Avg. Wt.}}{\text{label amount}} \times 0.863 \times \text{std. potency}$$

Dissolution study [15]

The dissolution test measures the rate of release of the drug from the dosage form *in vitro*, it is usually expressed as extent of dissolution (% drug content) occurring after a given time under specified conditions. For effective absorption of oral solid dosage form, simple disintegration of the dosage form is not adequate and the dissolution of the drug into the surrounding medium plays a vital role. Though dissolution is not a predictor of therapeutic efficacy it can be looked upon a tool which can provide valuable information about biological availability of drug and batch to batch consistency. Dissolution is considered as one of the most important quality control tests performed for pharmaceutical dosage form.

Procedure

The *in-vitro* dissolution study was carried out in the USP dissolution test apparatus, type II (paddle). One

tablet was placed in each of the six dissolution flasks containing 900 ml of dissolution medium, previously maintained at 37°C \pm 0.5°C.

After completion of each specified time interval, a portion of the solution was withdrawn from zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1 cm from vessel wall and filtered through 0.45 μ m membrane filter. The samples were collected at specified time intervals and diluted to required volume with dissolution medium.

The absorbencies of the standard and sample preparations were measured at 279 nm in 1 cm cells, with a suitable spectrophotometer using dissolution medium as blank. Finally the percentage drug dissolved of tapentadol hydrochloride tablets was calculated.

Calculation

$$\text{The percentage release of Tapentadol Hydrochloride} = \frac{\text{Test absorbance}}{\text{Std. absorbance}} \times \frac{\text{Std weight (mg)}}{100} \times \frac{\text{Sample dilution}}{\text{Test dilution}} \times \frac{900}{1} \times \text{Std.purity} \times \text{Label claim}$$

Stability studies [17-20]

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.

The International Conference on Harmonization (ICH) guidelines titled "Stability Testing of New Drug substance and Products" (Q1A) describes the stability test requirements for drug registration for drug registration applications in the European Union, Japan and The United States of America. ICH specifies the length of study and storage conditions.

RESULTS AND DISCUSSIONS:

Pre-formulation Studies:

Table 3: Organoleptic characteristics:

Properties	Results
Description	Crystalline
Taste and Odour	Highly bitter
Color	White

Table 4: Pre-formulation studies of Tapentadol hydrochloride

S. No	Tests	Results
1	Angle of repose	34.67 ⁰
2	Bulk Density	0.415 g/ml
3	Tapped Density	0.458 g/ml
4	Compressibility index	10.51%
5	Hausner's ratio	1.19

Based on the above pre-formulation results it was observed that the flow was poor and wet granulation method was suitable.

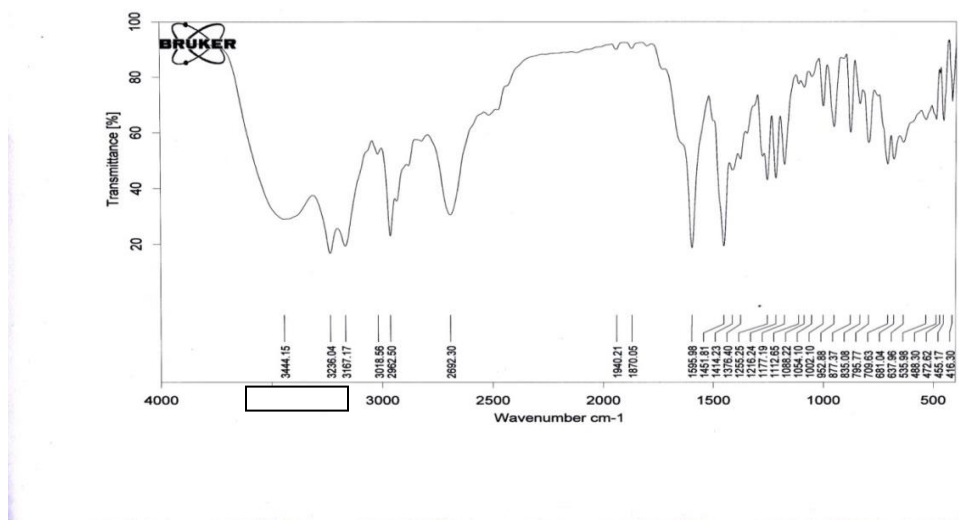
Solubility Profile:**Table 5: Solubility data of Tapentadol hydrochloride**

S. No	Buffers	Solubility (mg/mL)
1	Water	384.6
2	0.1N Hydrochloric acid	100.0
3	Acetate Buffer pH 4.5	142.9
4	Phosphate Buffer pH 6.8	200.0
5	Phosphate Buffer pH 7.8	333.3

From the above table results it is evident that solubility of Tapentadol hydrochloride is freely soluble in all dissolution media at different pH.

DRUG-EXCIPIENT COMPATIBILITY STUDY**FT-IR Spectrophotometry:**

The physical properties of total formulation were compared with those of pure drug and physical mixture. Here spectral changes in the mixture are the basis for the determination of compatibility. The obtained spectrums of pure drug and physical mixture of drug and all excipients were shown below.

**Fig.1: FT-IR Spectra of pure drug**

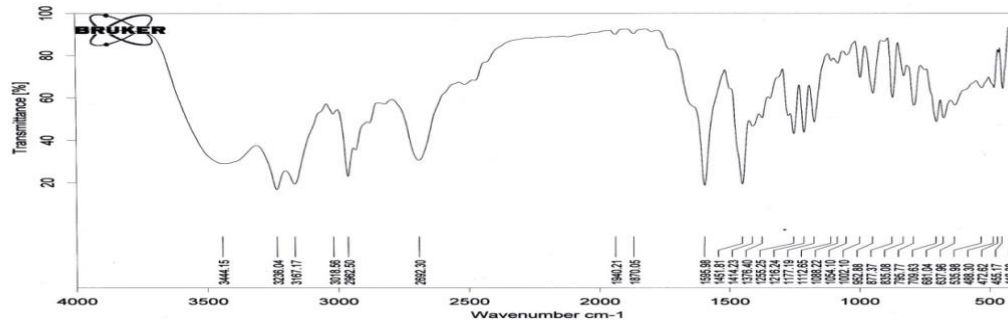


Fig2: FT-IR Spectra of physical mixture of pure drug and plasdone S630.

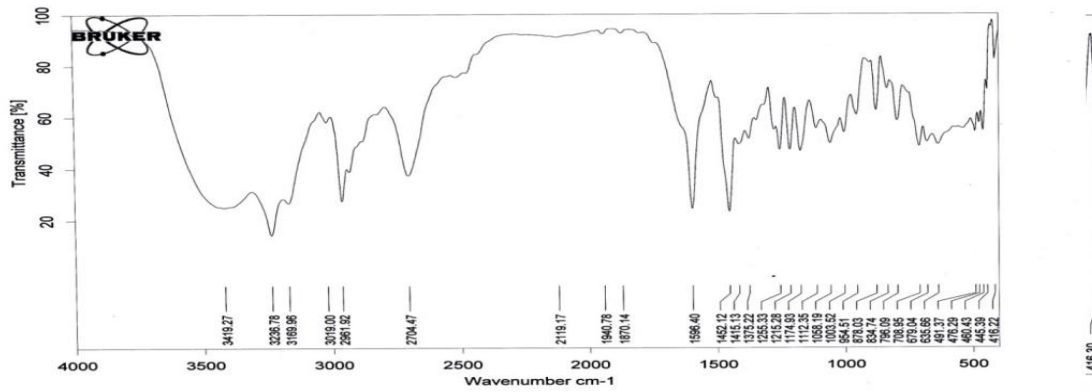


Fig.3: FT-IR Spectra of physical mixture of pure drug and microcrystalline cellulose PH 101

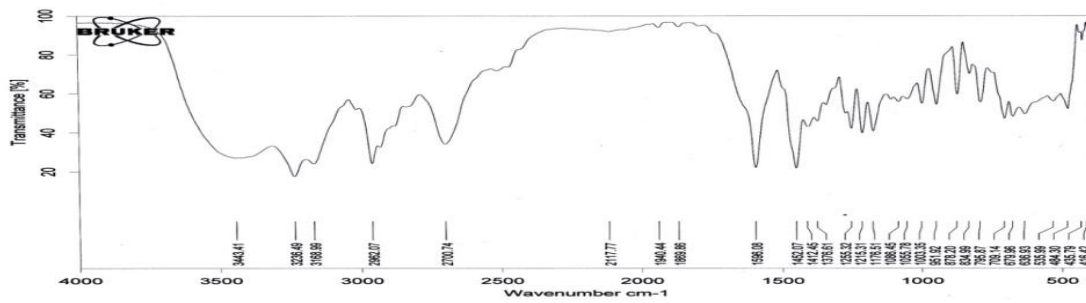


Fig.4: FT-IR Spectra of physical mixture of pure drug and HPMC K100M

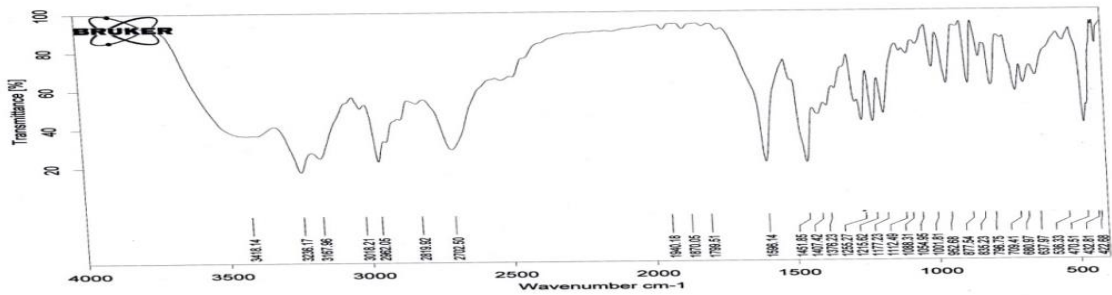


Fig.5: FT-IR Spectra of physical mixture of pure drug and HPC LF

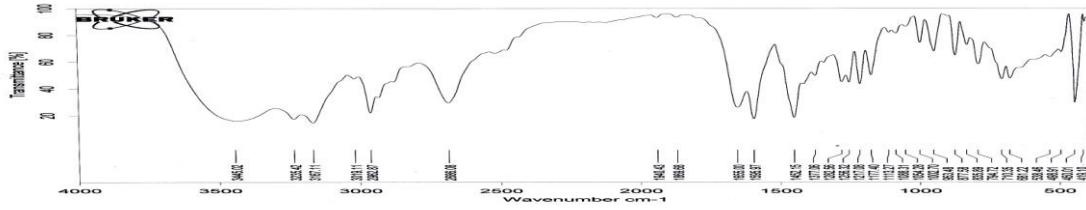


Fig.6: FT-IR Spectra of physical mixture of pure drug and PVP K30.

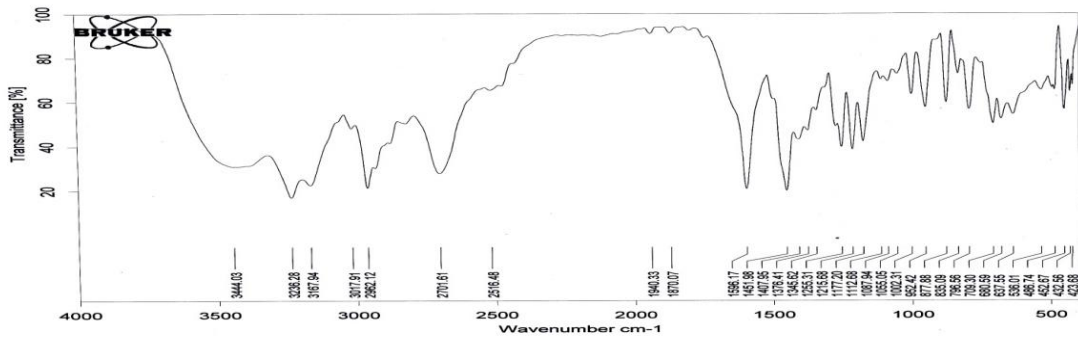


Fig.7: FT-IR Spectra of physical mixture of pure drug and Croscarmellose

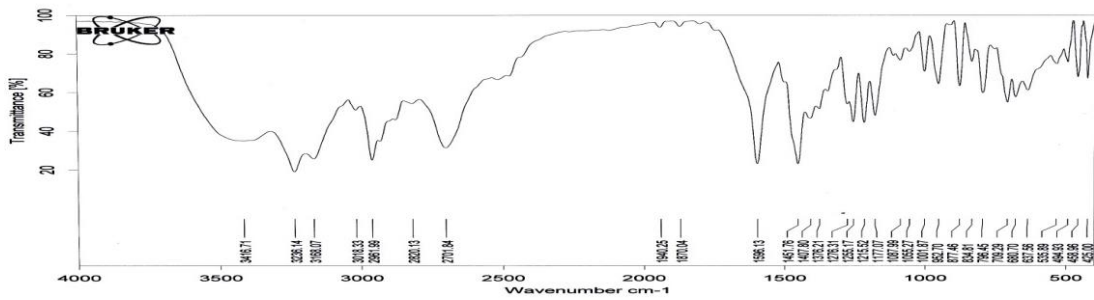


Fig.8: FT-IR Spectra of physical mixture of pure drug and xanthan gum

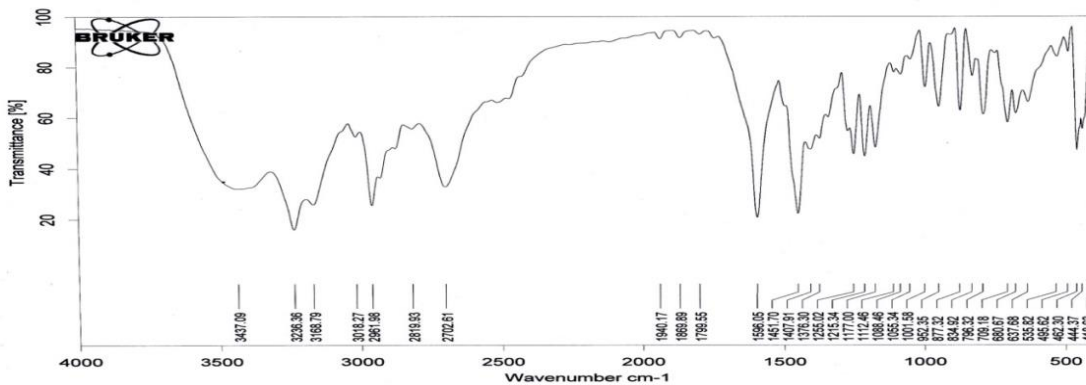


Fig.9: FT-IR Spectra of physical mixture of pure drug and Colloidal silicon oxide.

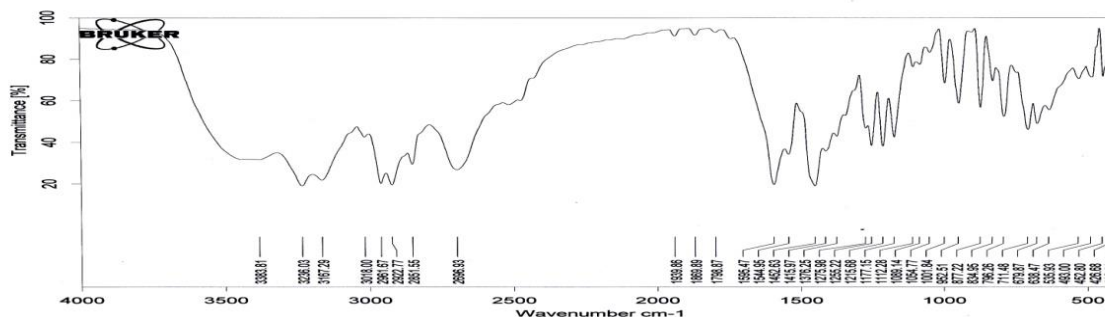


Fig.10: FT-IR Spectra of physical mixture of pure drug and magnesium stearate

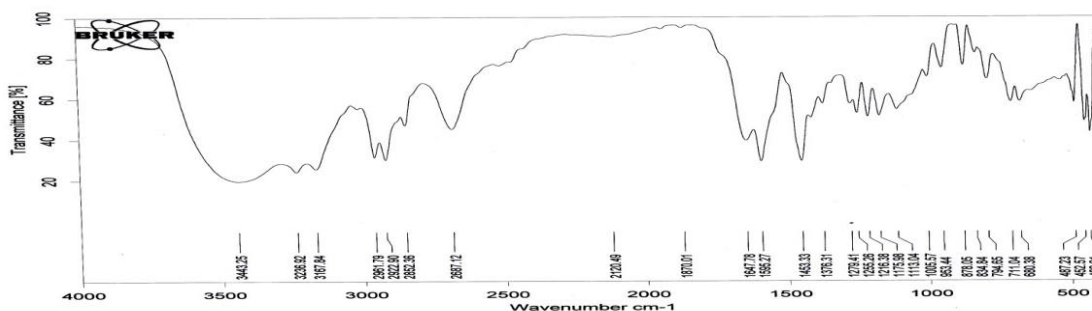


Fig.11: FT-IR Spectra of Physical mixer of Pure drug and all excipients.

FTIR spectra of Tapentadol Hydrochloride showed the peak at 3236 cm^{-1} due to the O-H stretching of hydroxyl group, peak at 2963 cm^{-1} due to the presence of aromatic C-H stretching, a sharp peak at 1596 cm^{-1} due to C=C stretching, a strong peak at 1255 cm^{-1} due to C-O stretching of phenol ring of the Tapentadol Hydrochloride and peak at 1216 cm^{-1} due to C-N stretching of amine.

Same peaks of drug were observed in physical mixture of drug and all excipients and also not shown any new peak in spectrum compared to drug which indicates the stable nature of drug. Hence it was expected that there is no interaction observed between the drug and used excipients.

Table 6: Micrometric properties of prepared granules:

Parameter	Angle of repose	Bulk density (mg/ml)	Tapped density (mg/ml)	Hausner's ratio	Compressibility index
F1	25.43^0	0.725	0.829	1.14	12.54
F2	26.46^0	0.734	0.854	1.16	14.05
F3	23.31^0	0.717	0.832	1.16	13.82
F4	27.29^0	0.724	0.843	1.16	13.63
F5	29.14^0	0.703	0.815	1.15	13.74
F6	24.54^0	0.719	0.835	1.16	13.89
F7	23.56^0	0.713	0.826	1.15	13.68
F8	23.49^0	0.701	0.814	1.16	13.88

All the formulations from F1 to F8 were found to show very good results for the above evaluation parameters. Compressibility index of all the formulations was found in between 12 to 15, indicates good compressibility index. Angle of repose of all formulations are found to be $< 30^\circ$, declares that all the formulations are possessing excellent flow properties and Hausner's ratio of all formulations was found to be 1.0 to 1.2, which satisfies the limits of compressibility.

Calibration Curve of Tapentadol Hydrochloride in phosphate buffer pH 6.8.

The construction of standard calibration curve of Tapentadol Hydrochloride was done by using phosphate buffer pH 6.8 as the medium. Tapentadol Hydrochloride in concentration of $100\mu\text{g/ml}$ in phosphate buffer pH 6.8 was scanned under UV-Visible spectrophotometer over a range from 400 nm to 200 nm and found to have the maximum absorbance at 279 nm.

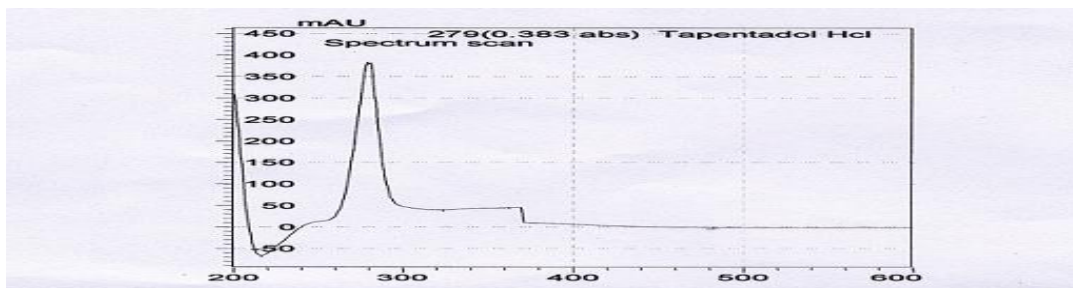


Fig.12: λ_{max} of the Tapentadol Hydrochloride Pure drug

The standard calibration curve of Tapentadol Hydrochloride in 6.8 phosphate buffer solution was developed in the concentration range of 50 – 250 $\mu\text{g/ml}$ with suitable dilutions of same medium and aliquots are observed for their absorbance under UV- spectrophotometer at an absorption maximum of 279 nm.

Calibration Curve of Tapentadol Hydrochloride in phosphate buffer pH 6.8.

Table 7: Standard calibration curve of Tapentadol Hydrochloride in phosphate buffer pH 6.8.

Concentration ($\mu\text{g/mL}$)	Absorbance (A.M \pm S.D)*
0	0.000
50	0.181
100	0.383
150	0.574
200	0.756
250	0.944

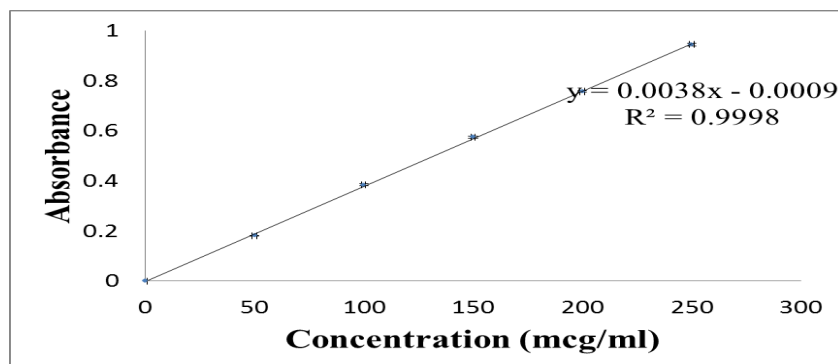


Fig.13: Calibration Curve of Tapentadol Hydrochloride in phosphate buffer pH 6.8.

Evaluation of the prepared tablets for physical parameters

All formulations (n = 5) were tested for physical parameters like hardness, thickness, weight variation, friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

i) ASSAY BY HPLC. Assay Of Impurities:

Assay of impurities by HPLC method

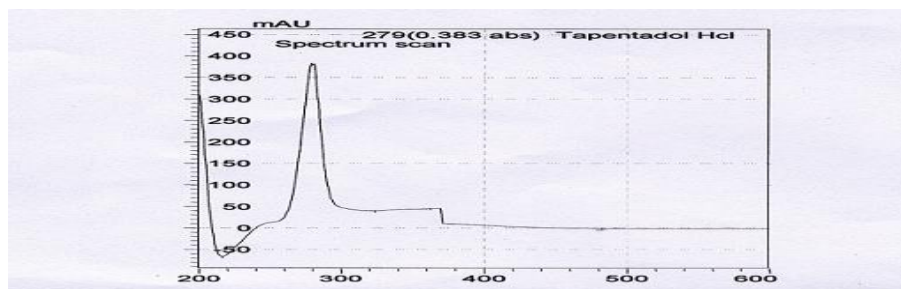
ii) ASSAY OF BLANK**iii)**

Fig.14: Assay of impurities by HPLC method

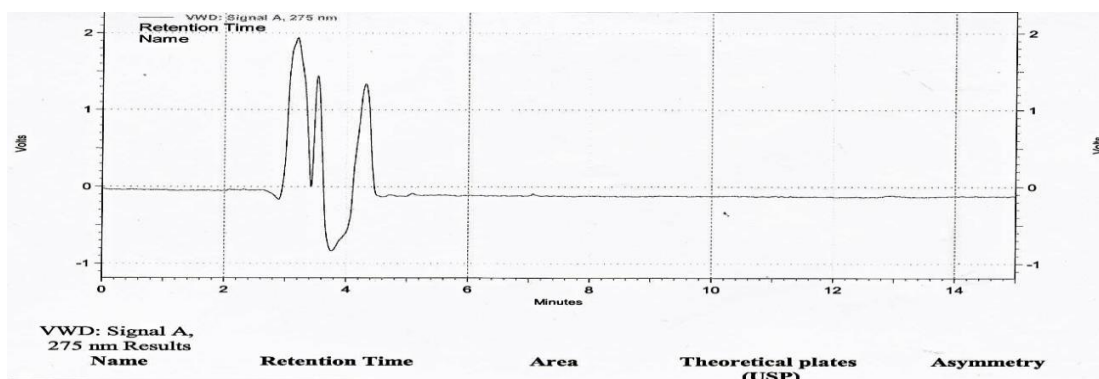


Fig.15: Assay of blank by HPLC method

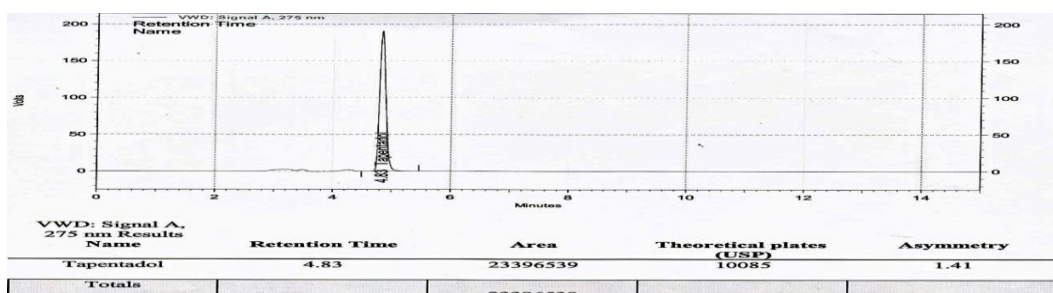
iv) ASSAY OF STANDARD

Fig.16: Assay of standard by HPLC method

v) ASSAY OF SAMPLE

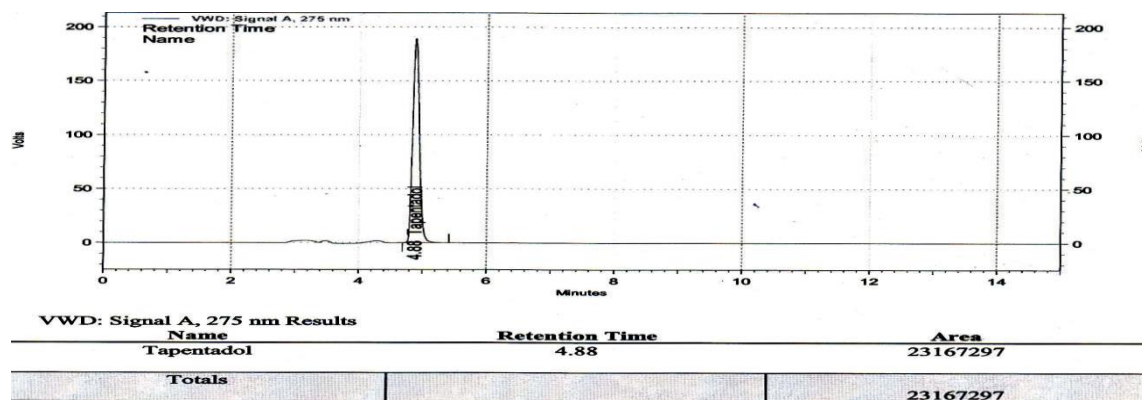


Fig.17: Assay of sample by HPLC method

Table 8: List of physical parameters of all formulations

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability	Drug content
F 1	600.8±1.02	5.1±.02	15±0.3	0.12%	99.01%
F 2	600.61±0.91	5.1±.02	15±0.3	0.16%	101.4%
F 3	600.01±0.99	5.1±.02	15.1±0.2	0.15%	99.35%
F 4	600.0±0.21	5.1±.02	15.2±0.2	0.15%	98.41%
F 5	600.9±1.21	5.1±.02	15.0±0.6	0.15%	99.51%
F 6	600.1±1.36	5.1±.02	15.0±0.7	0.15%	99.37%
F 7	600.8±0.98	5.1±.02	15.0±0.1	0.15%	100.5%
F 8	600.7±0.87	5.1±.02	15.0±0.4	0.15%	100.1%

***In-vitro* drug release study of Tapentadol hydrochloride in phosphate buffer pH 6.8**

The dissolution conditions used for studying the drug release from tablet of Tapentadol Hydrochloride are:

The samples were withdrawn at predetermined time points, and were analyzed spectrophotometrically at 279 nm.

Table 9: Cumulative percentage drug release from all formulations of Tapentadol hydrochloride extended release tablets.

Time (h)	Cumulative percentage of drug released								
	Innovator	F1	F2	F3	F4	F5	F6	F7	F8
0.5	13.23	11.8	13.4	13.4	13.4	13.5	13.5	13.6	13.2
2	34.5	27.7	28.4	28	29	30.1	32.3	35.3	35.5
4	55.2	41	49	48	49.8	51.2	52	53.2	54.6
6	69.4	53	59	59	61.3	63.2	66	67.6	68.7
8	81	59.4	61.2	61	66.9	73.2	75.5	78	79.9
10	91.7	62	67.4	65.5	69.9	74	79.2	86.7	89.5
12	97.2	74.5	80.2	76.8	79.9	81.4	85.5	91.5	95.2

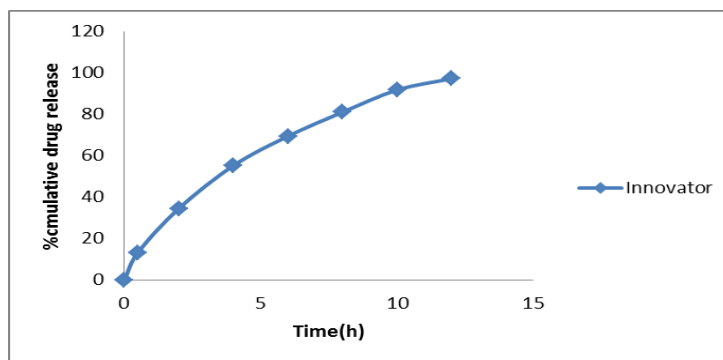


Fig.18: *In-vitro* dissolution profile of Tapentadol HCl from Innovator ER tablets

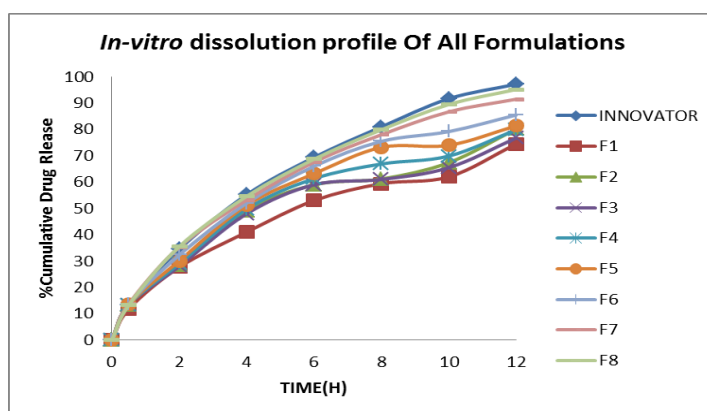


Fig.19: Comparative *In-vitro* dissolution profile of all formulations.

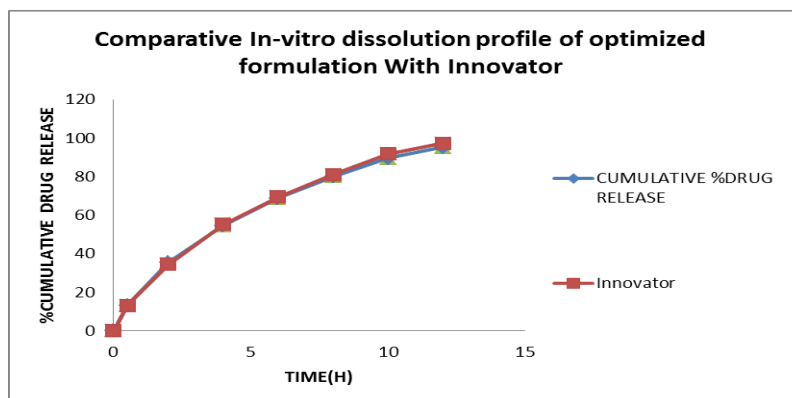


Fig.20: Comparative *In-vitro* dissolution profile of optimized formulation with Innovator

Dissolution profile of all formulations was compared. In F1 and F2 formulations the drug release was not complete as per specified time duration. The percentage drug release at the end of 12h was 74.5%, 80.2% for formulations F1 and F2 respectively. In formulations F3 to F6 the drug release was increased but not upto the mark. Formulation F7 was observed

to have the desired drug release profile by increasing the polymer concentration. Formulation F8 was observed to have drug release of 95.2% at the end of 12h by increasing the polymer concentration and the formulation F8 matches with the innovator drug release profile.

Table 10: *In-Vitro* drug release kinetics for optimized formulation: F8

Zero order data		First order data	Higuchi's data		Peppas's data	
Time (H)	Cumulative % release	Log Cumulative % Drug Release Remained	\sqrt{t}	Cumulative % release	Log time	Log cumulative % release
0.5	13.2	1.938519	0.707106	13.2	-0.30102	1.12057
2	35.5	1.809559	1.414214	35.5	0.30103	1.55022
4	54.6	1.657055	2	54.6	0.60206	1.737192
6	68.7	1.495544	2.44949	68.7	0.778151	1.83695
8	79.9	1.331960	2.828427	79.9	0.90309	1.9025
10	89.5	1.0211892	3.162278	89.5	1	1.9518
12	95.2	0.6812412	3.464102	95.2	1.079181	1.9786

Stability studies

The stability studies were carried out according to ICH guidelines for the optimized formulation i.e. F8. The stability studies were carried out under Accelerated stability studies ($40 \pm 2^\circ\text{C}/75\% \pm 5\% \text{RH}$). The tablets were packed in Al-Al blister packing and stored under 3 conditions. The tablets were analyzed at regular intervals of one month and evaluated for the tablet parameters like description, assay and dissolution. Sample were collected at an interval of 1, 2 and 3rd months and evaluated. Description, assay and dissolution profile of F8 stored under three conditions in 1M, 2M and 3M samples was found to be similar with that of initial samples.

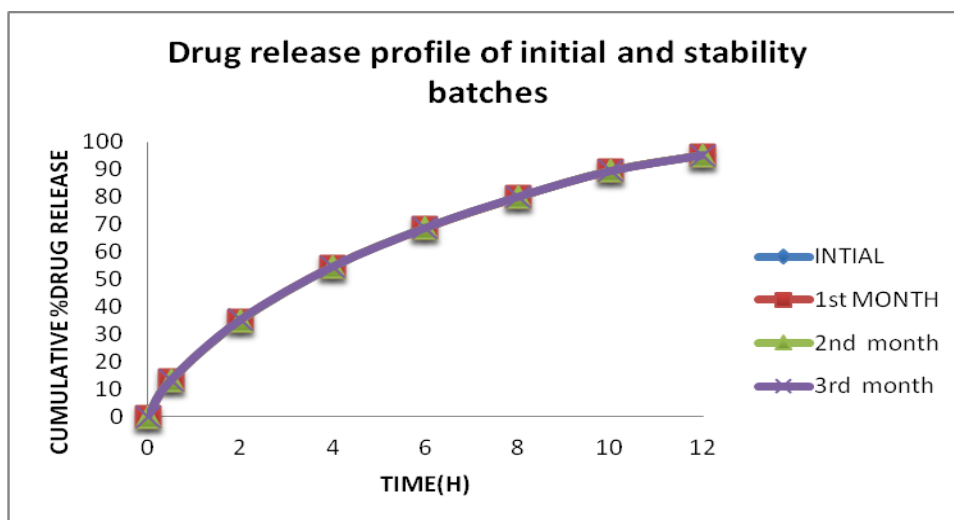


Fig.21: Comparison of drug release profile of initial and stability batches

The stability studies were carried out for a period of 3 months as per ICH guidelines, there was no significant change in dissolution profile and other parameters of the optimized formulation F8 and were found to be within acceptable limits.

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