FORMULATION, DEVELOPMENT & EVALUATION OF COMBINATION OF TRAMADOL & ACETAMINOPHEN FILM COATED TABLETS BY WET GRANULATION METHOD USING PVP K-30, MAIZE STARCH AS BINDER & HPMC E 15 AS FILM COATING POLYMER.

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ABSTRACT

Oral drug delivery is the largest and the oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration. The tablet coating is perhaps one of the oldest pharmaceutical processes still in existence. It offers many benefits namely – improving the analgesic quality of the dosage form, masking unpleasant order or taste, easing ingestion, improving product stability and modified the release characteristic of the drug. A Film coating is a barrier applied to oral medication that controls or masking unpleasant order or taste of the drug & as a rate controlling membrane for different formulation in digestive system where it is absorbed. . In the present investigation involves Design and Evaluation of Film coated tablet with using HPMC-E15 PVP K-30, Pregelatinized Starch and Sodium starch Glycolate by wet granulation method. Tablet was prepared using sodium starch Glycolate, Pregelatinized Starch, povidone k 30, maize starch, magnesium stearate and talc. In the Film coating process, coating polymer like HPMC-E15, plasticizer like PEG 6000, antitacking agent like talc and solvent like Isopropyl alcohol, Dichloromethane were important. The HPMC-E15 was used in the formulation ATT (139)201, 202, 203, and 204 respectively for coating polymer. The forth trial was performed by decreasing amount of Starch as binder in binder preparation with PVP K-30 for improving binding property and using water & IPA in ratio 1:1 for coating Solution. The in post compression parameter of coated tablet like hardness, thickness, average weight were found to be 116±12 N, 5.40±0.05 mm, and 634±3.5 mg respectively. In disintegration test, coated tablet disintegrate in neutral media in 4 min 34sec. The ATT (139)204 formulation showed cumulative % drug release 101.43±0.25. The superdisintegrant sodium starch glycolate was used in all formulation ATT (139)201, 202, 203, 204. In the experimental level, we have changed some parameters like concentration of binder in different formulation, composition of coating materials etc. Stability evaluations also confirmed that Formula ATT (139)204 was the best formulation. Thus Formula ATT (139)204 fulfills all the criteria for an optimized formulation.

Keywords: *Tramadol, Acetaminophen, HPMC-E15, PVP-K30, PEG 6000, Sodium Starch Glycolate, Pregelatinized Starch.*

INTRODUCTION

In the present scenario of pharmaceutical drug delivery system conventional pharmaceutical dosage forms are being replaced by new drug delivery systems. These are having edge over conventional systems in terms of many biopharmaceutical parameters and patient compliance. Over the hundred years tablet manufacturer have developed material and processes that can produce compressed tablet containing a precise amount of an active pharmaceutical ingredient (API) at high speed and at relatively low cost [1]. The

development in the field of API, excipients and tabletting machines or processing equipments during the past decade has made tablet manufacturing a science and tablets the most commonly used dosage form. Combination of one or more active ingredients gains importance in recent years to treat the various forms of diseases or to get the different therapeutic actions particularly from solid oral dosage form. In contemporary usage, the expression combination therapy most often refers to the simultaneous administration of two or more medications to treat a single disease, but the expression is also used when other types of therapy are used at the same time. A condition treated with combination therapy includes tuberculosis, leprosy, cancer, malaria, HIV/AIDS, hypertension, diabetes, Severe Pain etc [2]. Combination therapy may seem to be costlier than monotherapy in the short term but causes significant savings: lower treatment failure rate, lower case-fatality ratios, slower development of resistance and consequently, less money needed for the development of new drugs. Studies in analysis of dosage form consist of investigating the formulation during the development with respect to physical and chemical properties. It is a one of the critical in-vitro study of the dosage form. Formulation development of the generic product to be submitted in the regulated market involves numerous studies to be conducted with supporting analytical data.

Studies executed during the development are

- API characterization
- Study of excipients profile.
- Drug - excipient compatibility studies.
- Selection of excipient based on compatibility data
- Selection of process based on characterization of active ingredient.
- Selection of packing material based on photo stability and moisture pick up study.
- Stability of dosage form at different temperature & humidity conditions.

Tramadol (±)-*cis*-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its empirical formula is $C_{16}H_{25}NO_2 \cdot HCl$, with a molecular weight of 299.84. Tramadol Hcl is a white, crystalline powder. Freely soluble in water and in methanol; very slightly soluble in acetone. Tramadol is a centrally acting synthetic opioid analgesic [3]. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests [4].

The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound. Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Acetaminophen *N*-(4-hydroxyphenyl)-. Its empirical formula is $C_8H_9NO_2$, with a molecular weight of 151.16. Acetaminophen is a white, odorless, crystalline powder, having a slightly bitter taste. Freely soluble in alcohol; soluble in boiling water and in 1 N sodium hydroxide.

Acetaminophen is a non-opiate, non-salicylate analgesic [3, 4].

EFFECT OF BINDERS ON TABLET PROPERTIES

Binders are added to a material to increase bonding. Granulations with a more homogenous distribution of binder in the granules generally produce tablets of a higher mechanical strength than granulations with a peripheral localization of binder. Studies on the effect of various formulations and processing factors on the properties of some tablets by various authors revealed that at a constant moisture level and packing fraction, an increase in binder concentration generally results in increased tensile strength, disintegration and dissolution times (decreased dissolution rates), reduced capping tendency, ER/PC (elastic recovery/plastic compression) ratio and the brittle fracture index value (BFI- a measure of the lamination tendency of tablets) of the tablets. Increasing molecular mass of binder (bloom number for

gelatin for example) increases tablet tensile strength when compressed to fixed apparent density [5]. The radial strength is little affected but the axial tensile strength is increased by increased concentration of binder to strength greater than the radial strength. The results have been explained in terms of the effects of moist and binder bridges on bonding of particles in tablets. The role of binders in the moisture-induced hardness increase in compressed tablets containing lactose as a major excipient was studied. Results showed that the increase in moisture-induced hardness in compressed tablets is related linearly to the amount of moisture loss from the tablets after compression. It was also reported that the magnitude of the hardness increase is related to the type and concentration of the binder used in wet granulation. This moisture-induced hardness increase in the tablets had no effect on the tablet disintegration time and in vitro drug dissolution [5,6].

Here we use PVP K-30 & Maize Strach as Tablet binder using distilled water in various formulations. The HPMC E 15 was suitable coating polymer in different formulations. Polyethylene glycol (PEG) is used for the preparation of solid dispersions. A particular advantage of PEGs for the formation is that they have good solubility in many organic solvents. The melting point of PEGs lies below 65 0C in all cases which is advantageous for the manufacture of immediate release dosages forms. Additional attractive features of PEGs include their ability to solubilize some compounds and also improve compound wettability. Therefore, in the present study, PEG 6000 was chosen as a suitable polymer for the preparation of different formulations [6].

EXPERIMENTAL SECTION

☞ Materials

Tramadol & Acetaminophen was a purchased from BEC chemicals, Hyderabad, poly ethylene glycol 6000 was purchased from Signet chemical, Povidone K 30 from Shinestu chemicals, Sodium hydroxide (Finar chemicals ltd. Ahemdabad), Sodium Starch Glycolatefrom Signet, Pregletanized Strach from Venus Pharma, Microcrystalline cellulose from FMC, Ireland, Colloidal silicon dioxide (Aerosil 200) from Degussa and Magnesium stearate from Ferro industrias quimicas(Portugal). All required chemicals were analytical grade [7].

☞ Compatibility Studies

A Compatibility study focuses on a binary mixture of drug with the excipient being investigated is intimately mixed, and the ratio of drug to excipient is often 1:1 with or without added moisture. The mixture is stored at an elevated temperature in capped vials. The result of the interaction between the active drug and excipients may be determined by techniques such as DSC, TLC, HPLC, or solution colorimetry [8].

Procedure

1. Prepare Drug and Excipients mixture (1:1 mixture)
2. The Drugs and Excipients individually and in combination shall be subjected for accelerated and long term and freeze study conditions along with control samples and study at fixed intervals of initial, 15 days and 30 days.
3. The recommended drug- excipients ratios for solid dosage forms are tabulated below.
4. After exposure of samples to the study conditions, the following parameters should be analyzed.(Compatibility Studies shown in Table No.11, 12, 13, 14, & 15. [9]

☞ Preparation of Standard Calibration Curve.

➢ Calibration Curve of Tramadol in Phosphate buffer (6.8 pH)

20 mg of Tramadol was taken in 100 ml of phosphate buffer (pH 6.8) and was kept in ultra sonifier until the complete dissolution of the drug. From the stock solution suitable dilutions were prepared in decreasing order which were analyzed UV Visible spectrophotometer at 270.5 nm and absorbance values was recorded as shown table no.1. Then a standard calibration curve was constructed using MS Excel as shown in fig no.1[10] .

➢ **Calibration Curve of Tramadol in 0.1N Hcl (1.2 pH)**

20 mg of Tramadol was accurately weighed and transferred to previously dried 100 ml volumetric flask. Drug was dissolved in 0.1N HCl solution. The solution was suitably diluted with 0.1NHCl solution to get standard concentration of 10, 20, 30, 40, 50, µg/ ml. absorbance was measured at 270.5 nm UV visible spectrophotometer and absorbance values was recorded in table no.2. Then a standard calibration curve was constructed using MS Excel as shown in fig no.2 [11].

➢ **Calibration Curve of Acetaminophen in Phosphate buffer(6.8 pH)**

20 mg of Acetaminophen was taken in 100 ml of phosphate buffer (pH 6.8) and was kept in ultra sonifier until the complete dissolution of the drug [12]. From the stock solution suitable dilutions were prepared in decreasing order which were analyzed UV Visible spectrophotometer at 243.5 nm and absorbance values was recorded as shown table no.3. Then a standard calibration curve was constructed using MS Excel as shown in fig no.3.

➢ **Calibration Curve of Acetaminophen in 0.1N Hcl (1.2 pH)**

20 mg of Acetaminophen was accurately weighed and transferred to previously dried 100 ml volumetric flask. Drug was dissolved in 0.1N HCl solution. The solution was suitably diluted with 0.1NHCl solution to get standard concentration of 10, 20, 30, 40, 50, µg/ ml. absorbance was measured at 243.5 nm UV visible spectrophotometer and absorbance values was recorded in table no.4. Then a standard calibration curve was constructed using MS Excel as shown in fig no.4 [13].

☞ **IR spectroscopy:**

The IR spectrum of each drug was recorded using Perkin Elmer- FTIR Spectrometer Spectrum RX-I. About 5 mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted using a hydraulic press at a pressure of about 100-150 kg cm^{-2} for 3 minutes. The resultant disc was mounted in a suitable holder in a Perkin Elmer IR spectrophotometer. The resultant spectra were compared with standard spectra. The results of IR spectroscopy for Drug A(Tramadol) & B(Acetaminophen) are given in Fig no. 5 & 6 on pg no. 18 [14].

☞ **Method of Preparation**

❖ **Dispensing**

Carried out the dispensing of active Pharmaceutical Ingredient and excipient in separate dispensing booth. Wore personal protective gloves were worn when required during all stages of dispensing [14].

❖ **Sifting**

Sift issued quantity of Acetaminophen, Tramadol Hydrochloride, Microcrystalline Cellulose and Calcium Hydrogen Phosphate through 40 # and starch through 60#. (Sifting of material shown in tab no.

❖ **Binder Preparation**

Issued quantity of purified water is heated in a vessel and boiled at 70ºC. Purified water is taken in a SS container, issued quantity of Sodium Methyl Hydroxy benzoate and Sodium Propyl Hydroxybenzoate, PVP K-30 and issued quantity of Maize starch is added in the same solution. Slurry is made and this slurry is added in the boiling water of the Paste Preparation Vessel. The slurry should be thick and transparent [15].

❖ **Mixing/Granulation**

The sifted materials from the above step are taken in Rapid Mixer Granulator (RMG). Premixing takes place for 5 minutes. Add the above paste and mix for 11 minutes in slow speed. Add issued quantity of purified water if required for better Granulation[10, 15].

❖ **Drying**

Loaded the FBD bowl containing wet mass in FBD and started the FBD as per set recipe. Dried the granules in FBD till outlet temperature reached up to 35±2°C or LOD reached within 2.0 % to 4.0 % w/w on Infrared moisture Balance at 105°c. Checked the inlet and outlet temperature (if required) after every 15 minutes. After some time of drying, predried granules were sifted through 18# using vibro sifter then removed the FBD bowl from FBD. Collected the random sample of dried granules and checked the LOD on moisture balance.
(LOD of different formulations is shown in table no.7.

❖ **Sizing of Dried Granules**

The material from FBD is unloaded and passed through mutimill sieve 2.0 mm. The sifted granules are milled through 18# and weighed [16].

❖ **Blending & Lubrication**

The unloaded granules are charged into the blender. Issued quantities of Purified Talc & Magnesium Stearate are shifted through 60# & sift Colloidal Anhydrous Silica through 30#. The lubricating granules are charged into the blender without magnesium stearate and the blender is started for 10 minutes. Then magnesium stearate is added and the blender is started for 3 minutes [16,17].

❖ **Compression**

Adjust the compression machine and compress the approved lubricated granules. Collect the tablets in IPC bin and weigh.

❖ **Machine Setting**

Tooling – D
Upper Punch – 17*7 mm, Caplet, Standard concave, breakline punches.
Lower Punch – 17*7 mm, Caplet, Standard concave, plain Punches.
Dies - Suitable for above punches[18].

❖ **Compression**

Compressed the lubricated materials in 12 station compression machines with using 17*7 mm Standard concave breakline at upper punch & plain in Lower punch.

❖ **Coating**

Issued quantity of Isopropyl Alcohol is taken in SS vessel and issued quantity of Hypromellose E-15 is added with continuous stirring. Issued quantity of Isopropyl Alcohol is taken in another vessel and issued quantity of color Yellow oxide of iron (Ferric Oxide) is added to it with continuous stirring. Both the solutions from above are mixed with continuous stirring and issued quantity of Dichloromethane is added to it and mixed [18,19]. Issued quantity of Dichloromethane is taken in the SS Vessel and issued quantity of Macrogol 6000 and mixed with continuous stirring. The solutions from above are mixed through colloid mill and then filtered through 200#. The weighed compressed tablets are charged into the coating pan or Auto- coater, the spray gun is set and the air pressure rate is adjust it properly. The bed temperature is kept at not more than 40ºC. After completion of the coating, the sample was packed in double polyethylene bag.

❖ **Coating Process Parameter**

- Inlet Temperature - 45ºC
- Bed Temperature - 35ºC
- Pump Speed – 1 rpm
- Coating Pan speed – 28 rpm

☞ ***In-Vitro* Dissolution Studies:**

Dissolution for Acetaminophen and Tramadol Hydrocholoride Tablets

Medium : 0.1 N HC; 900 ml
Apparatus : Paddle: 50 rpm
Time : 30 minutes

Sample solution:
Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Standar dSolution:
0.36mg/ml of USP Acetaminophen RS and 0.04 mg/ml of USP Tramadol Hydrochloride RS in medium.
Mobile Phase:
Acetonitrile and buffer solution (1:40).
Chromatographic System
Mode : LC
Detctor : UV 270.5nm for Tramadol & 243.5 for Acetaminophen

Column : 4.6mm*15cm, 5-µm packing L7
Column Temperature: 25^0c
Flow Rate: 1.0ml/min.
Injection Size: 25µL
SystemSuitability
Sample: Standard Solution
[Note_ The relative retention times for acetaminophen and Tramadol Hydrochloride are about 0.5 & 1.5 recpectively.]
Suitability Requirement
Resolution: NLT 5.0 between the peaks of Acetaminophen & Tramadol Hydrochoride.
Relative Standard Deviation: NMT 2.0 % for both Acetaminophen &Tramadol HydrochloridePeaks.

In Vitro drug release study is the important part for all solid oral dosage forms and other dosage forms. it is used in all phases of drug development . In the pharmaceutical industry, drug dissolution testing is routinely used to provide critical in vitro drug release. At early stages of development, in vitro dissolution testing guides the optimization of drug release from formulations. Over the past 50 years, dissolution testing has also been employed as a quality control (QC) procedure, in R&D to detect the influence of critical manufacturing variables and in comparative studies for in vitro-in vivo correlation (IVIVC) [19,20].

The FDA guidance on dissolution testing for immediate release solid oral dosage forms includes the use of the Biopharmaceutics Classification System (BCS) guidelines for biorelevant dissolution tests, which is based upon API solubility and permeability. According to the BCS guidelines, *in- vitro* dissolution testing may be a useful tool to forecast the in vivo performance of drug products and potentially reduce the number of bioavailability/bioequivalence studies required [20,21].

- ***In Vitro* Drug Release of Film Coated Tablet of Acetaminophen & Tramadol.**

The in vitro dissolution studies for all the formulations were carried out in following steps, using USP apparatus type II (paddle) at 50 rpm. The dissolution medium consisted of hydrochloric acid buffer solution (pH - 1.2) 900 ml for 2 hours maintained at 37 °C ± 0.5 °C. The drug release at different time (5, 10, 15, 20, 30) minutes intervals was measured by UV-1700 UV-visible spectrophotometer at 270.5nm for Tramadol & 243.5 for Acetaminophen (Hydrochloric acid buffer solution pH - 1.2). The release studies were conducted in triplicate (6 tablets in each set) and dissolution procedure are given in the table no.11[22].

RESULTS AND DISCUSSION

❖ LIST OF TABLES

Table No. 1 Concentration versus Absorbance of Tramadol in pH 6.8 Buffer at 270.5 nm.

S. No.	Conc.(µg/ml)	Abs.(nm)
1	00	0.000
2	10	0.1243
3	20	0.2387
4	30	0.3600
5	40	0.4798
6	50	0.6209

Table No. 2 Concentration versus Absorbance of Tramadol in HCL 1.2 pH at 270.5 nm.

S. No.	Conc.(µg/ml)	Abs.(nm)
1	0	0.000
2	10	0.149
3	20	0.302
4	30	0.441
5	40	0.585
6	50	0.738

Table No. 3 Concentration versus Absorbance of Acetaminophen in pH 6.8 Buffer at 243.5 nm.

S. No.	Conc.(µg/ml)	Abs.(nm)
1	0	0.00
2	2	0.143
3	4	0.267
4	6	0.391
5	8	0.523
6	10	0.659

Table No. 4 Concentration versus Absorbance of Acetaminophen in HCL 1.2 pH at 243.5 nm.

S. No.	Conc.(µg/ml)	Abs.(nm)
1	0	0.00
2	2	0.10
3	4	0.22
4	6	0.34
5	8	0.46
6	10	0.60

Table No. 5 Bulk characterization of Granules

S.No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of repose(^{0})
ATT(139)201	0.528±0.02	0.562±0.03	12.338±0.15	1.14±0.12	27.24±2
ATT(139)202	0.519±0.02	0.598±0.03	13.333±0.10	1.15±0.12	24.00±2
ATT(139)203	0.498±0.02	0.585±0.03	14.238±0.12	1.18±0.12	22.19±2
ATT(139)204	0.512±0.02	0.592±0.03	12.128±0.22	1.15±0.12	28.10±2

Table No. 6 Particle size analysis of Granules

S. No.	Sieve No.				
	20#	40#	60#	80#	100#
ATT(139)201	18.16±0.22%	7.32±0.23%	11.32±0.12%	4.78±0.07%	38.64±0.19%
ATT(139)202	16.29±0.27%	6.42±0.32%	13.26±0.21%	6.42±0.09%	41.66±0.27%
ATT(139)203	17±0.52 %	5.36±0.34%	14.48±0.15%	7.36±0.10%	50.32±0.14%
ATT(139)204	16.89±0.31%	5.64±0.12%	13.89±0.30%	6.78±0.05%	51.32±0.31%

Table No. 7 Loss on Drying of Granules

S No	Formulation	LOD (%)
1	**ATT(139)201**	2.87±0.25%
2	**ATT(139)202**	2.53±0.18%
3	**ATT(139)203**	2.43±0.32%
4	**ATT(139)204**	2.68±0.25%

Table No 8 Post Compression Characterizations of Formulated Tablets

Parameters	Formulation Code			
Formulation	**ATT(139)201**	**ATT(139)202**	**ATT(139)203**	**ATT(139)204**
Average weight (mg)	634±2	637±2.2	633±2.5	635±2.8
Hardness (N)	107±7	109±10	115±12	119±15
Thickness (mm)	5.50±0.04	5.4±0.05	5.34±0.05	5.47±0.05
Disintegration time (min)	3min.10 sec	3min. 48 sec	7min.2sec	5min. 14 sec

Table no. 9 Stability Data of Batch ATT (139)204 [37.5/325mg]

Product: Drug A(Tramadol) + Drug B(Acetaminophen) Film coated Tablets						
Label claim : Each Film coated tablet contains Drug A 37.5mg & Drug B 325mg						
Batch No. : SB3 (Pack: Alu - Alu Blister)						
					2 M	
Sr. No.	**Tests**	**Limits**		**Initial**	**40°C/75 %RH**	
1.	**Description**	A caplet shaped, biconvex, film coated tablet with light Yellow color layer, Breakline on upper side & plane on lower side.			Complies	
2.	**Dissolution**	**Time**	**Limits %**	**% Mean**	**% Mean**	
				MS	**SB204**	**MS**	**SB204**
Drug A		**30min.**	**NLT 90%**	99.91%	99.01%	99.21%	98.31%
Drug B		**30min.**	**NLT 90%**	99.80%	99.35%	98.91%	98.84%
Assay							
3.	**Drug A**	90 – 110%		98.66%	97.35%	97.90%	96.81%
	Drug B	90 – 110%		99.22%	100.9%	98.8%	99.30%

*__SB__: stability batch; *__MS__: marketed sample

[Note:-
No significant changes observed in Tablet description, Assay and Drug dissolution from initial to 2M stability study of Batch ATT(139)204

Table no. 10 Details of *In-Vitro* Drug Release Studies

Apparatus used	USP type II dissolution test apparatus
Dissolution medium	0.1N Hydrochloric acid
Volume of dissolution medium	900 ml
Temperature	37±0.5 ^{0}C
Speed of paddle	50 rpm
Sampling interval	5 min
Sample withdrawn volume	10 ml
Absorption measurement	270.5nm for Tramadol & 243.5nm for Acetaminophen

Table No.11 % Cumulative Drug Release Profile of Film Coated Tablets of Tramadol & Acetaminophen in 0.1N HCL medium at 1.2 pH

Time(Min)	ATT(139)201		ATT(139)202		ATT(139)203		ATT(139)204	
	Trama	Aceta	Trama	Aceta	Trama	Aceta	Trama	Aceta
0	0	0	0	0	0	0	0	0
5	82.8	85.0	86.8	81.8	85.6	87.8	83.1	89.5
10	90.2	93.1	96.7	92.9	96.5	96.4	98.2	94.4
15	96.1	98.4	97.9	97.6	98.8	98.8	99.0	99.6
20	98.4	99.9	99.7	99.2	99.8	100.1	100.1	100.8
30	100.6	100.0	102.4	99.8	101.3	101.0	101.7	101.9

Table No. 12 Compatibility Studies at Initial Stage for Drug A (Tramadol)

S.No	Name of drug/ Excipient	Ratio	Related Substance (Total Impurity)	Moisture Content	Appearance
1.	Drug A	5 g.	2.60%	2.45%	Off white
2.	Drug A + (MCC) Microcrystalline Cellulose-101	1:1	2.67%	2.49%	Off white
3.	Drug A + Maize Starch	1:1	2.77%	2.42%	Off white
4.	Drug A + sodium starch Glycolate	1:1	2.63%	2.51%	Off white
5.	Drug A + Povidone k-30	1:1	2.59%	2.43%	Off white
6.	Drug A + Talc	1:1	2.71%	2.38%	Off white
7.	Drug A + Pregelatinized Starch(Lycatab)	1:1	2.61%	2.53%	Off white
8.	Drug A + Magnesium Stearate	1:1	2.72%	2.48%	Off white
9.	Drug A + HPMC E-15	1:1	2.68%	2.39%	Off white
10.	Drug A + Polyethylene Glycol 6000	1:1	2.70%	2.33%	Off white
11.	Drug A + Titanium	1:1	2.63%	2.41%	Off White

	Dioxide(BP)				
12	Drug A + FD &C Yellow Oxide of Iron	1:1	2.48%	2.39%	Yellow

Table No. 13 Compatibility Studies at Initial Stage for Drug B(Acetaminophen)

S.No	Name of drug/ Excipient	Ratio	Related Substance (Total Impurity)	Moisture Content	Appearance
1.	Drug B	5 g.	2.60%	2.45%	Off white
2.	Drug B + (MCC) Microcrystalline Cellulose-101	1:1	2.67%	2.49%	Off white
3.	Drug B + Maize Starch	1:1	2.77%	2.42%	Off white
4.	Drug B + sodium starch Glycolate	1:1	2.63%	2.51%	Off white
5.	Drug B + Povidone k-30	1:1	2.59%	2.43%	Off white
6.	Drug B + Talc	1:1	2.71%	2.38%	Off white
7.	Drug B + Pregelatinized Starch(Lycatab)	1:1	2.61%	2.53%	Off white
8.	Drug B + Magnesium Stearate	1:1	2.72%	2.48%	Off white
9.	Drug B + HPMC E-15	1:1	2.68%	2.39%	Off white
10.	Drug B + Polyethylene Glycol 6000	1:1	2.70%	2.33%	Off white
11.	Drug B + Titanium Dioxide(BP)	1:1	2.63%	2.41%	Off White
12	Drug B + FD&C Yellow Oxide of Iron	1:1	2.48%	2.39%	Yellow

Table No. 14 Compatibility Studies at 40°C/75% RH for Drug A (Tramadol)

S.No	Name of drug/ Excipient	Ratio	Related Substance (TotalImpurity)	Moisture Content	Appearance
1.	Drug A	2:0	2.54%	2.42%	Off white
2.	Drug A + (MCC) Microcrystalline Cellulose-101	1:1	2.38%	2.61%	Off white
3.	Drug A + Maize Starch	1:1	2.50%	2.77%	Off white
4.	Drug A + sodium starch Glycolate	1:1	2.59%	2.79%	Off white
5.	Drug A + Povidone k-30	1:1	2.38%	2.40%	Off white

6.	Drug A + Talc	1:1	2.49%	2.39%	Off white
7.	Drug A + Pregelatinized Starch(Lycatab)	1:1	2.69%	2.69%	Off white
8.	Drug A + Magnesium Stearate	1:1	2.77%	2.55%	Off white
9.	Drug A + HPMC E-15	1:1	2.98%	2.58%	Off white
10.	Drug A + Polyethylene Glycol 6000	1:1	2.26%	2.48%	Off white
11.	Drug A + Titanium Dioxide(BP)	1:1	2.79%	2.58%	White
12	Drug A + FD &C Yellow Oxide of Iron	1:1	2.68%	2.46%	Yellow

Table No. 15 Compatibility Studies at 40°C/75% RH for Drug B (Acetaminophen)

S.No	Name of drug/ Excipient	Ratio	Related Substance (Total Impurity)	Moisture Content	Appearance
1.	Drug A	2:0	2.54%	2.42%	Off white
2.	Drug A + (MCC) Microcrystalline Cellulose-101	1:1	2.38%	2.61%	Off white
3.	Drug A + Maize Starch	1:1	2.50%	2.77%	Off white
4.	Drug A + sodium starch glycolate	1:1	2.59%	2.79%	Off white
5.	Drug A + Povidone k-30	1:1	2.38%	2.40%	Off white
6.	Drug A + Talc	1:1	2.49%	2.39%	Off white
7.	Drug A + Pregelatinized Starch(Lycatab)	1:1	2.69%	2.69%	Off white
8.	Drug A + Magnesium Stearate	1:1	2.77%	2.55%	Off white
9.	Drug A + HPMC E-15	1:1	2.98%	2.58%	Off white
10.	Drug A + Titanium Dioxide(BP)	1:1	2.79%	2.58%	White
11.	Drug A + FD &C Yellow Oxide of Iron	1:1	2.68%	2.46%	Yellow

LIST OF FIGURES

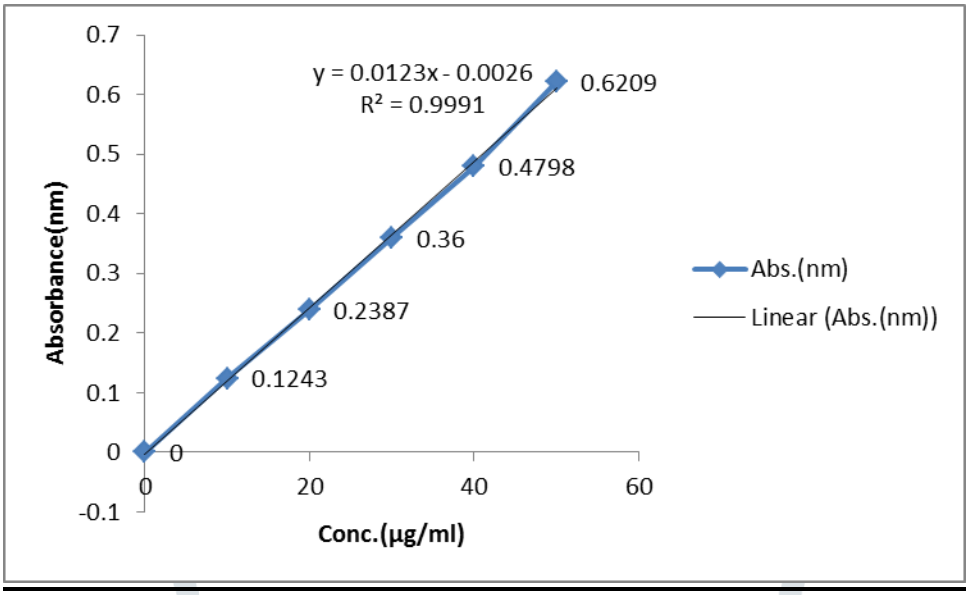

Figure No. 1 Standard Curve of Tramadol in buffer of pH 6.8 at 270.5 nm.

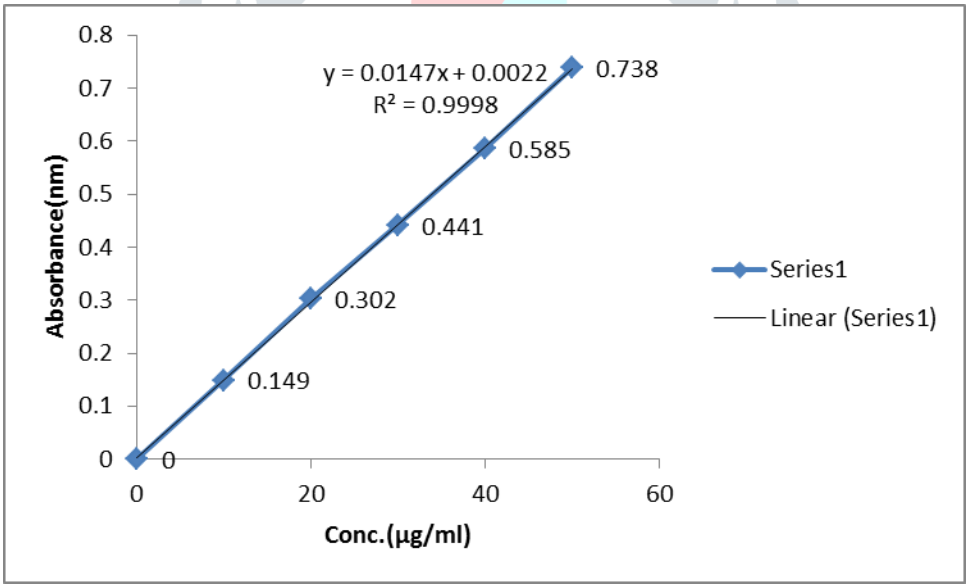

Figure No. 2 Standard Curve of Tramadol in Buffer of 1.2pH at 270.5 nm.

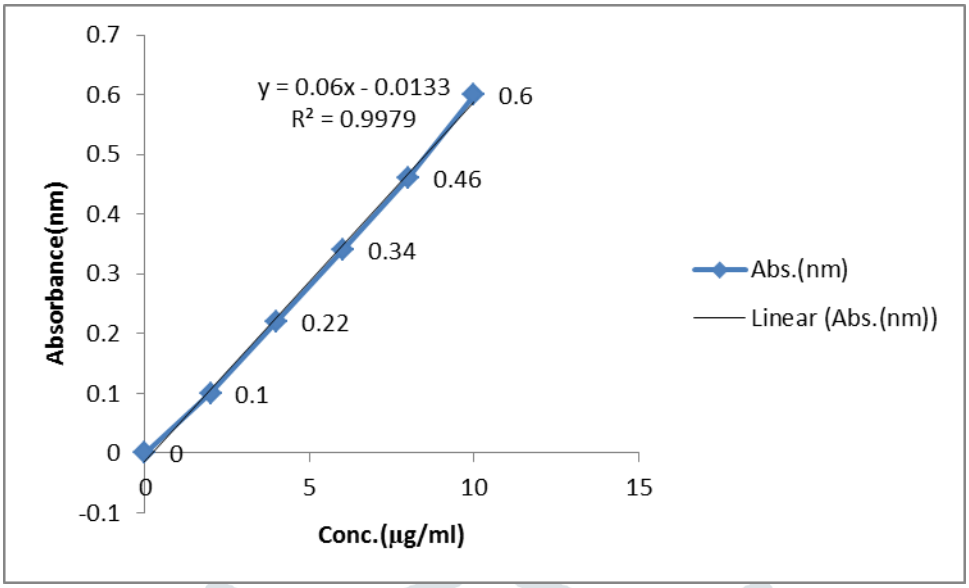

Figure No. 3 Standard Curve of Acetaminophen in Buffer of 1.2pH at 243.5 nm.

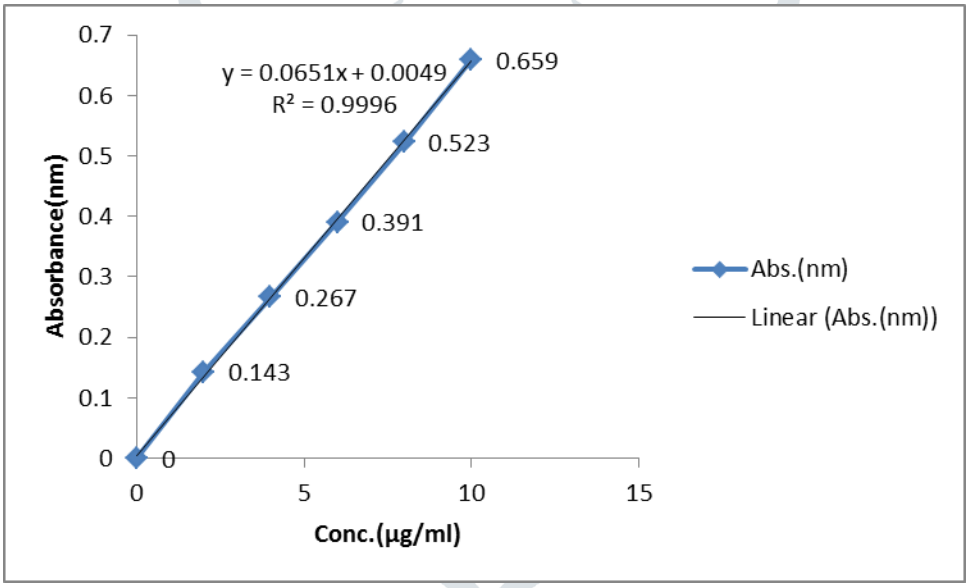

Figure No. 4 Standard Curve of Tramadol in Buffer of 6.8 pH at 243.5 nm.

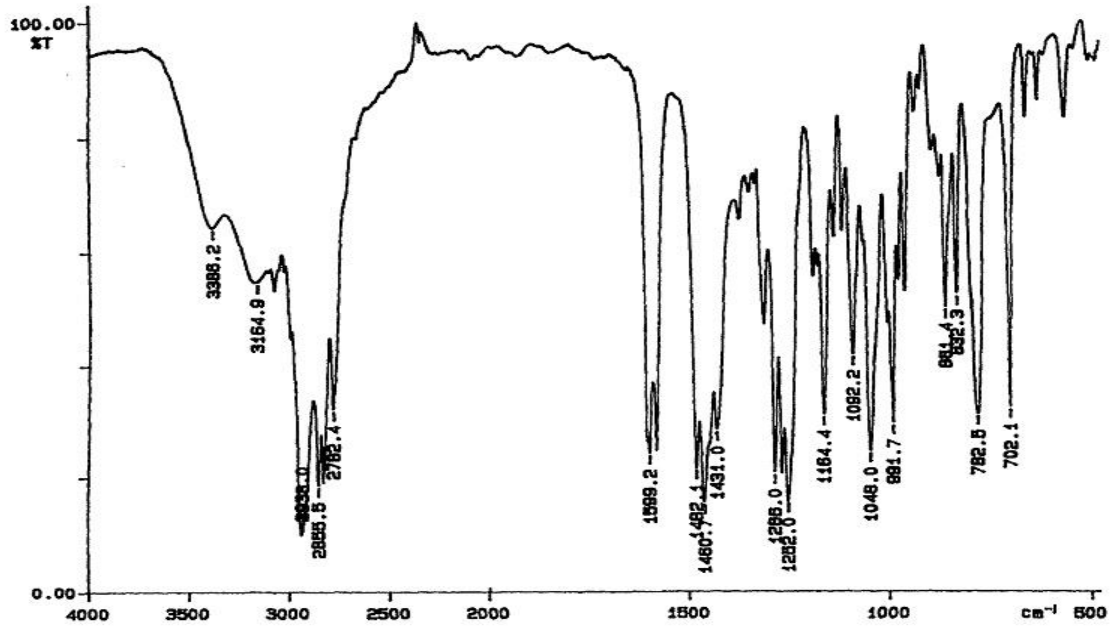

Figure No. 5 IR Spectrum of Tramadol.

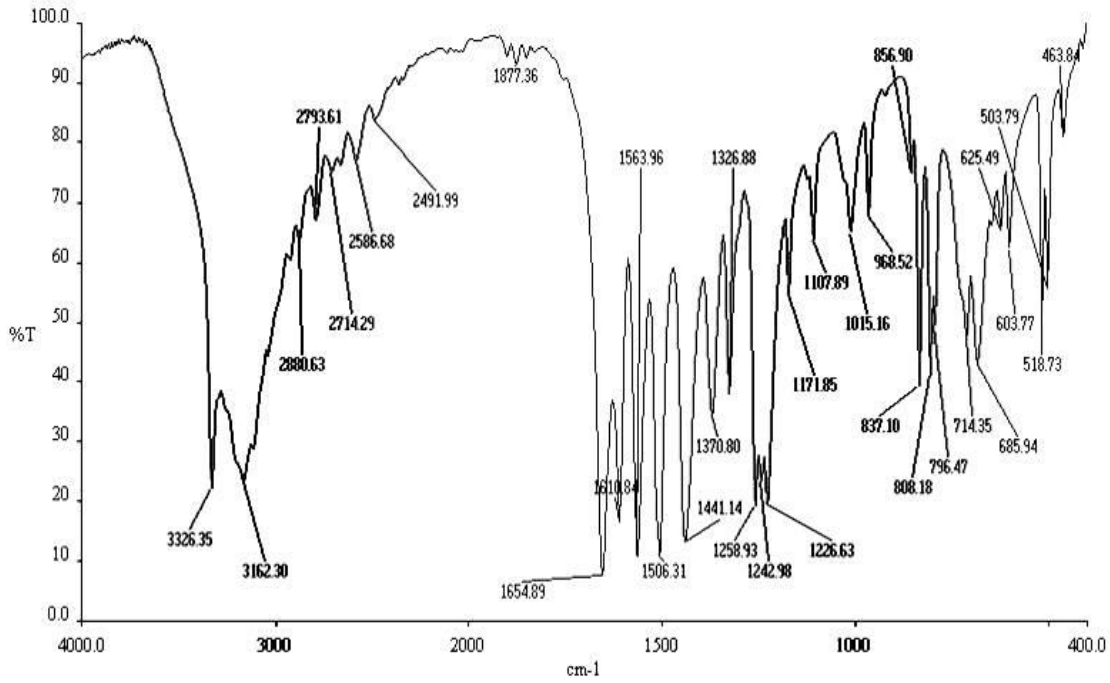

Figure No. 6 IR Spectrum of Acetaminophen.

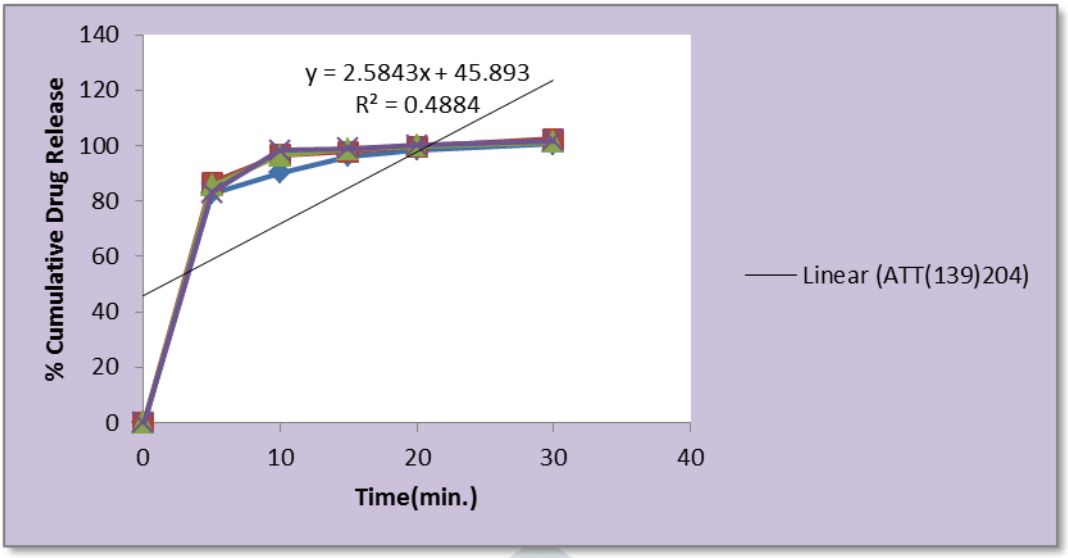

Figure No. 7 % Drug Release Profile of Film coated Tablet of Tramadol at pH 1.2

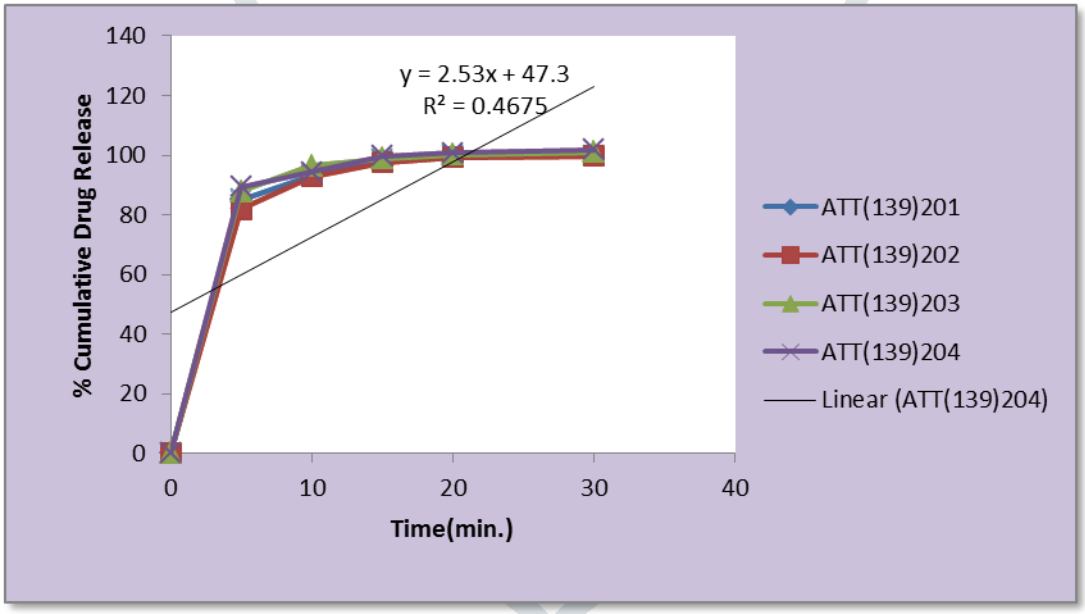

Figure No. 8 % Drug Release Profile of Film coated Tablet of Acetaminophen at pH 1.2

❖ EVALUATION OF TABLETS:

Physical evaluation of tablets:

- **Appearance: Caplet** shaped, Light Yellow colored, tablet with breakline on upper side and plane on lower side.
- **Thickness:** Tablets were selected randomly from each batch at regular intervals and thickness was measured in mm by using digital Vernier caliper.
  Acceptance criteria: 5.40±0.3mm
- **Hardness test:** Tablets were selected randomly from each batch at regular intervals and hardness was measured in Newton (N) by using Dr. Schleuniger hardness tester. For each batch a minimum of 10 tablets were tested.
  Acceptance criteria: 110-125 N.
  The lowest hardness at which the tablets pass the friability test was used to decide the hardness range.

- **Friability test:** A sample of 10 tablets were taken randomly from each batches and placed in the friabilator (Electro lab) and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were de-dusted and weighed again. The % friability was measured using formula [23],

  % F = W_0-W/ W_0 x 100

  Where, % F = Friability in percentage

  W_0 = Initial weight of tablets

  W = Weight of tablets after revolutions

  Acceptance criteria: A maximum loss of weight (from a single test or from the mean of the three tests) not greater than 1%.
- **Weight variation:** 20 tablets were randomly selected, de-dusted and weighed individually. The average weight of 20 tablets was calculated. % weight variation from average weight of tablet was calculated using following formula: [24]

  % Weight variation = {(Individual tablet weight- Avg. weight of 20 tablets) / Avg. weight of 20 tablets} x 100

  Acceptance criteria: The batch pass the weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than percentage shown in below table and none deviates by more than twice the percentage shown:

Table .16 Percentage deviation allowed by weight variation test as per IP 2010

Average weight of tablets (mg)	Percentage deviation
80 mg or less	10 %
More than 80 mg and less than 250 mg	7.5 %
250 mg or more	5 %

- **Disintegration test:**

Apparatus: Disintegration test apparatus
Reagent: Purified water
Procedure: The assembly was suspended in the specified liquid medium in a 1000 ml beaker. The volume of liquid was taken such that when the assembly was in highest position the wire mesh was at least 25 mm below the surface of the liquid and when the assembly was in lowest position the wire mesh was at least 25 mm above the bottom of the beaker. One tablet was placed into each of the tube of the assembly and disk was added to each tube. The apparatus was operated for specified time and temperature at 37 ± 2^0 C. Time for complete disintegration of tablet was noted down[16, 23].

Acceptance criteria: The tablets pass the test if Drug A+ Drug B layer disintegrates in less than 15 minutes.

❖ Chemical evaluation of tablets:

- **Assay:** 10 tablets were weighed and assayed as per in house test developed. The assay was carried out using HPLC method.

  Acceptance criteria: The average drug content of drug A and drug B should be within the range of 90-110% .
- **Dissolution:**

  Dissolution testing for the amount of drug-substances (i.e. Drug A and Drug B) released was studied using the following dissolution parameters: [11, 17]

Table.17 Dissolution parameters and specifications for Drug A(Tramadol) and Drug B(Acetaminophen).

Drug Name	Apparatus	Speed(RPM)	Medium	Vol(ml)	Acceptance Criteria
Drug A	USP-II Basket	75	0.1 N HCl	900 ml	NLT 90%
Drug B	USP-II Basket	75	0.1 N HCl	900 ml	NLT 90%

Acceptance criteria : As given table no.10.

- **Content uniformity:** The content of active ingredients in each of 10 intact dosage units taken at random was determined using the assay method developed in house.
  Acceptance Criteria: The preparation complies with the test if each individual content is within 90 to 115 percent of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75 to 125 percent of the average content. If one individual content is outside the limits of 90 to 115 percent of the average content but within the limits of 75 to 125 percent, repeat the determination using another 20 dosage units. The preparation complies with test if not more than one individual contents of the total sample of 30 dosage units is outside 90 to 115 percent of the average content and none is outside the limits of 75 to 125 percent of the average content [16, 18].

RESULT AND DISCUSSION

❖ Stability Result

From the above results of stability batch no. **ATT (139)204,** it was concluded that no significant changes observed in Tablet description, Assay and Drug dissolution from initial and 2M stability study at **40°C/75 %RH.**

❖ Physical Characterization

Characterization of the drug for different parameters were carried out including identification, related substance, heavy metal, and melting point by different method and the result was found to be acceptable. Further this was characterized for drug solubility study in the different solvent including water, acetone, alcohol and dilute mineral. Later after it was observed that Tramadol & Acetaminophen was freely soluble in Water and Acetone, sparingly soluble in dilute mineral acid, and insoluble in Methylene Chloride. Particle size analysis of Tramadol & Acetaminophen was performed using vibratory shifter and the result was found to be within limit. Bulk characterization was carried out to observe the flow property of active drug that have great effect during formulation process. This includes bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose. The result of bulk characterization was found to be acceptable and had Acceptable flow property.

❖ *Invitro* Results

Dissolution analysis was employed to assess the effect of the Film coat composition and coverage levels on the release of the formulations. *In vitro* drug release was carried out for different formulations with different coating composition in film coated tablets (ATT (139)201-04) respectively in 0.1 N HCl for 2 Hours. Figure 6.1 & 6.2 compares the dissolution profile of Film coated Tramadol & Acetaminophen tablets prepared using different coating materials in HCL buffers. It is evident from the figure that all the four formulations demonstrated excellent Dissolution Property in acid medium. This observation is anticipated, as these Immediate Film coated polymers have shown the various effects in earlier reports.

The formulations ATT(139)201, 202, 203, & 204 showed % cumulative drug release in acid medium for 30 minutes for Tramadol are 100.6, 102.4, 101.3, 101.7 & for Acetaminophen are 100.0, 99.8, 101.0, & 101.9 respectively.

All the formulations showed % cumulative drug releases in prescribed limits, but formulation ATT (139)204 Show more appropriate results as compare to others in all tests. The drug release varies with varying the formulation composition concentration in different formula. The layer buildup by many types of agents like polymer, plasticizer, anti tacking agent and solvents. These agents are very important for Film coating.

SUMMARY AND CONCLUSION

Acetaminophen has an analgesic, antipyretic & Anti-inflammatory actions, while Tramadol is used in mild to moderate pain. Film coated tablet of combination of this drugs was prepared in this study. This study set out to improve the physical and chemical characteristics of the present formulation using an appropriate experimental design and to improve the release of drug. The material and method were selected to meet the quality and to make cost effective.

Preformulation studies were performed to characterize the drug and excipient for best formulation. Many methods are used in preformulation study like identification of drug, solubility of drug, angle of repose, bulk density, tapped density, particle size analysis, carr's index and compatibility study. In identification of drug, The infrared absorption spectrum of a sample should concordant with spectrum obtained from Tramadol & Acetaminophen working standard and the principle peak in the chromatogram obtained with the test solution in similar in retention time and size to the principle peak in the chromatogram obtained with reference solution. And drug practically insoluble in Methylene chloride and freely soluble in water, Isopropyl alcohol also in dichloromethane.

Angle of repose 56^0±0.21, bulk density 0.476±0.10gm/ml , tapped density 0.724±0.12gm/ml, Carr's index 34.286±0.25% for Drug A(Tramadol) and similarly Angle of repose 69^0±0.21, bulk density 0.390±0.10gm/ml , tapped density 0.704±0.12gm/ml, Carr's index 44.53±0.25% for Drug B(Acetaminophen).

In the above study of drug characterization different parameters of drug were carried out including identification, related substance, heavy metal, and melting point by different method and the result was found to be acceptable.

Film coated tablet was prepared by wet granulation method and the most important ingredient in Film coating polymer is HPMC-E15 play main role in formulation. Many methods were used in characterization of Film coated tablet. Pre compression and post compression. In pre compression, sieve Analysis, angle of repose, bulk density, tapped density, carr's index and In post compression, hardness, thickness, friability and disintegration time [13, 19].

Various formulations were prepared to finalize the binder concentration for the best and economic formulation. The tablet was prepared by wet granulation method by preparing PVP-K30 with Maize Starch translucent slurry. After that extragranular material was added and compressed to form tablet. In first formulation, the in post compression parameter of coated tablet like hardness, thickness, average weight were found to be 117±7 N, 5.40±0.04 mm, and 634±2 mg respectively. In disintegration test, coated tablet disintegrate in acid media in 15±0.30 min.

In second trial batch we use Sodium Starch Glycolate (Glyclyos) & Pregelatinized Starch (Lycatab) for improving binding property and using water & IPA in ratio 3:2 for coating Solution then preformed dissolution and disintegration studies. And result obtained that tablet disintegrate in acid media 0.1N HCL. The in post compression parameter of coated tablet like hardness, thickness, and average weight were found to be 115±10 N, 5.42±0.05 mm, and 635±2.2 mg respectively. In disintegration test, coated tablet disintegrate in acid media in 4 min 17 sec.

The third trial was done by using additional PVP K-30 as binder in binder preparation for improving binding property and using water & IPA in ratio 2:3 for coating Solution. The in post compression parameter of coated tablet like hardness, thickness, average weight were found to be 113±12 N, 5.45±0.05 mm, and 634±2.5 mg respectively. In disintegration test, coated tablet disintegrate in acid media in 5 min 4sec.

The forth trial was performed by decreasing amount of Starch as binder in binder preparation with PVP K-30 for improving binding property and using water & IPA in ratio 1:1 for coating Solution. The in post compression parameter of coated tablet like hardness, thickness, average weight were found to be 116±12 N, 5.40±0.05 mm, and 634±3.5 mg respectively. In disintegration test, coated tablet disintegrate in acid media in 4 min 34sec.

The coating weight gain is around 2.1% of dry polymer weight 6.000 mg on 620mg tablet. The talc content in our formulation is low (about 6%). Anti- adherents aid in reducing tackiness & substrate sticking during coating. Though not significantly noticeable, there might be changes of tablet sticking during coating which are subsequently responsible for uncoated microspores in tablet coat try to minimize this tablet sticking by keeping optimum talc concentration (50% of dry polymer).

In last formulation we took all ingredients like 3% of Dry polymer (HPMC E15) and anti tacking agent like talc of dry polymer. The concentration of HPMC E15 took 2-3 % in the forth trial. The in post compression parameter of coated tablet like hardness, thickness, average weight were found to be 116±12 N, 5.40±0.05 mm, and 634±3.5 mg respectively. In disintegration test, coated tablet disintegrate in acid media in 4 min 34sec and result obtained % cumulative drug release 101.43±0.25%. Later after stability studies was also performed at the accelerated stage for 2 months and the result found to be there was no more change in the physical and chemical properties and was acceptable[20, 23].

Conclusion

I have concluded that the Film coated tablet of combination of Tramadol & Acetaminophen can be the better and economic formulation in all our market that prepare Film coated tablet of same formulation for Mild to Moderate pain. Although numerous commercial formulations of same formulation are available in the market. Film coated tablet of Tramadol & Acetaminophen was prepared using Isopropyl Alcohol, distilled water and HPMC-E15 with PEG 6000 are not available so far.

Present study was carried out with following objectives:

- Select the active and excipient material.
- Preformulation study of drug and drug with excipient.
- Formulation of tablet.
- Evaluation of tablet.
- To improve the release of dosage form.
- To overcome the relative substance.
- To formulate an economic formulation and process.
- To mask the organoleptic properties of formulation.

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