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FORMULATION AND EVALAUTION OF TRILAYER EXTENDED RELEASE TABLET

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ABSTRACT

The aim of present study is to develop a trilayer extended release tablet by using Bupropion, Naltrexone drug combination. In the present investigation authors have tried to explore trilayer extended release tablet by using Microcrystalline cellulose (PH 101). Wet granulation method is used for the formulation of trilayer tablet

KEYWORDS: Trilayer, extended release, generic drug etc.

INTRODUCTION TO GENERIC DRUGS

Pharmaceuticals have made a major contribution to improving the health status of patients over a past few decades. At the same time, its expenditure has increased rapidly, with spending on medicines outpacing economic growth in many countries. Many economists have speculated that, if spending on healthcare continues to increase at the current rate, the economies of most countries will be severely affected. Most government have, therefore, begun to implement cost containment measures to slow the rate of healthcare spending and have concentrated to a larger degree of pharmaceutical spending. Since generic are marked at substantially lower prices than the original brand –name products and, with the rising cost of healthcare; this has made them an attractive option to healthcare providers and government.

The US is by far the world's largest generic market, and the combination of the country's free prizing rules and pro-generic environment make it an extremely attractive prospect for foreign investors, despite the intensity of the competition During 2005-07 two thirds of the major international acquisitions involving a US pharmaceutical company involved a foreign company acquiring a US firm. However, the level of competition in the US is increasingly putting a brake on growth, driving consolidation and global expansion. Therefore, the

relatively less penetrated European markets provide a more attractive prospect for domestic players.

The FDA's use of the word "Identical" is very much a legal interpretation, and is not literal in most cases, generic products are available once the patent protections afforded to the original developer have expired .when generic products becomes available, the market competition often leads to substantially lower prices for both the original brand name product and the generic forms.

USFDA requires generic drug to have the same quality, strength, purity, and stability, as brand name drug. The manufacturer of the generic drug product has certain constraints in formulation development that differ from the formulation development of candidate drug product. For example a generic drug manufacturer may have to use the same or similar inactive ingredient or Excipients as in the brand formulation. Generic drugs are usually sold for significantly lower prices than their branded equivalents. One reason for the relatively low prize of generic medicines is that competition increase among producers when drugs are protected by patents .Companies incur fewer costs increasing generic drugs (only the cost to manufacture ,rather than the entire cost of development and testing) and are therefore able to maintain profitability at a lower price.

1. Types of Layered Tablets

a. Bilayer Tablet[7,8,9]

Bilayer tablets are suitable for sequential and simultaneous release of two different API's. In this two layers are immediate release.

Bilayer tablet is suitable mean of to deliver two drugs at one time without any dynamic and pharmacological interaction. The bilayer tablet containing subunits that may be either the same drug (homogeneous) or different drugs (heterogeneous).

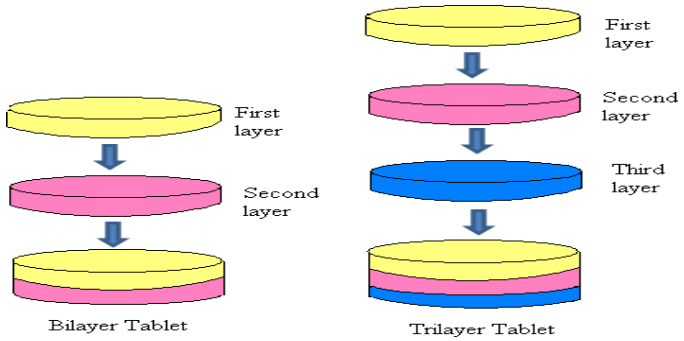

Fig. 1: Types of Multi-layered tablet.

Homogenous type[7,8,9]

Bilayer tablets are preferred when the release profiles of the drugs are different from one another. Bilayer tablets allows for designing and modulating the dissolution and release characteristics. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner.

Heterogeneous type[7,8,9]

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances.

2. Drug Candidate

Table 1: Drug profile of Drug – Bupropion.

Attribute	Description
Description	White powder
Solubility	Soluble in water, in 0.1 N HCl and in alcohol
PH	4.98 (aq.Solution)
pKa	8.1
Lop p	2.8
Hygroscopicity	Not hygroscopic
Polymorphism	Hetero product of crystalline form I
Isomerism	Contain one chiral central and the configuration at chiral center
Therapeutic category	Anti-depressant

Table2: Drug profile of Drug – Naltrexone.

Attribute	Description
Description	White powder
Solubility	Soluble in water, in 0.1 N HCl and in alcohol
PH	7.2 (aq.Solution)
pKa	9.1
Lop p	1.9
Hygroscopicity	Hygroscopic
Polymorphism	Hetero product of crystalline form II
Isomerism	Contain chiral central
Therapeutic category	Opioid Antagonist

Formulation of different batches by Wet Granulation:

Table 3: Formulation of batch T1 to T4.

Sr. No	Ingredients	(Quantity in mg/tablet)			
		T1	T2	T3	T4
Layer I : Drug-Bupropion					
Intra-granular					
	Drug –Bupropion	90	90	90	90
	Microcrystalline cellulose (PH 101)	135	135	135	135
Granulation					
	L-Cysteine HCL	2.5	5.0	7.5	10
	HPMC 6 Cps	5	5	5	5
	Purified Water	Qs	Qs	Qs	Qs
Extra-Granular					
	Hydroxy propyl cellulose (Klucel HXF)	52.5	55.0	47.5	45.0
	Magnesium stearate	5	5	5	5
TOTAL		**290**	**295**	**290**	**290**
Layer III : INNERT LAYER					
Intra-granular					
	Microcrystalline cellulose (PH 102)	105	105	105	105
	Sodium Starch Glycolate	9	9	9	9
	Magnesium stearate	0.50	0.50	1.0	1.0
TOTAL		**115**	**115**	**115**	**115**
Layer II : Drug-Naltraxone					
Intra-granular					
	Drug-Naltraxone	8	8	8	8
	Microcrystalline cellulose (PH 101)	80.25	80.25	80.00	80.00
	Lactose monohydrate	99	99	91.50	91.5
Granulation					
	Edetate Disodium	1.0	2.5	5.0	5.0
	HPMC 6 Cps	5	5	2.5	2.5
	Purified Water	Qs	Qs	Qs	Qs
Extra-Granular					
	Hydroxyl propyl cellulose(Klucel HXF)	35	35	50	75
	Colloidal silicon dioxide	8.5	8.5	8.5	8.5
	FD&C Blue #2 Aluminum Lake	0.5	0.5	0.5	0.5
	Magnesium stearate	4	4	4	4
TOTAL		**240**	**240**	**250**	**275**
Coating Material					
	Opadry II Blue	20	20	20	20
	Purified Water	80	80	80	80
TOTAL		**665**	**670**	**675**	**700**

Table 4: Formulation of batch T5 to T8.

Sr. No	Ingredients	(Quantity in mg/tablet)			
		T5	T6	T7	T8
Layer I : Drug-Bupropion					
Intra-granular					
	Drug-Bupropion	90	90	90	90
	Microcrystalline cellulose (PH 101)	135	135	135	135
Granulation					
	L-Cysteine HCL	12.5	15.0	17.5	20.0
	HPMC 6 Cps	5	5	5	5
	Purified Water	Qs	Qs	Qs	Qs
Extra-Granular					
	Hydroxy propyl cellulose (Klucel HXF)	42.5	40.0		35.0
				37.5	
	Magnesium stearate	5	5	5	5
TOTAL		**290**	**290**	**290**	**290**
Layer II : INNERT LAYER					
Intra-granular					
	Microcrystalline cellulose (PH 102)	105	105	105	105
	Sodium Starch Glycolate	9	9	9	9
	Magnesium stearate	1.0	1.0	1.0	1.0
TOTAL		**115**	**115**	**115**	**115**
Layer III : Drug-Naltraxone					
Intra-granular					
	Drug-Naltraxone	8	8	8	8
	Microcrystalline cellulose (PH 101)	80.00	80.00	80.00	80.00
	Lactose monohydrate	91.5	91.5	91.5	91.5
Granulation					
	Edetate Disodium	5.0	5.0	5.0	5.0
	HPMC 6 Cps	2.5	2.5	2.5	2.5
	Purified Water	Qs	Qs	Qs	Qs
Extra-Granular					
	HPMC K100 LVCR	75	75	75	75
	Colloidal silicon dioxide	8.5	8.5	8.5	8.5
	Magnesium stearate	0.5	0.5	0.5	0.5
TOTAL					
Coating Material					
	Opadry II Blue	20	20	20	20
	Purified Water	80	80	80	80
TOTAL		**645**	**650**	**655**	**710**

3. Manufacturing procedure by Wet Granulation:

Lyer I Sifting

1. Sift microcrystalline cellulose (PH 101)& API through ASTM # 20 mesh.

Dry mixing

2. Transfer the sifted mass into RMG bowl and dry mixing for 10 minutes at slow Impeller speed and chopper off.

LOD = 2.0%&BD = 0.7 gm/ml

Binder solution preparation

3. Dissolve L-Cysteine HCL and HPMC 6 Cps in purified water at room temperature.

Granulation

Table 5: granulation process parameter.

Sr.no.	Process	Time(seconds)	Impeller	Amperes	chopper	Amperes
1	200 ml Binder addition	120	150	1.2	slow	1.2
2	Kneading	60	150	1.3	slow	1.4
3	50 ml water addition	60	150	1.2	slow	1.2
4	Kneading	30	150	1.2	slow	1.4

Total binder addition = 200 ml Total granulation time = 4.5 min.

Drying

5. Transfer material into RD and continue the drying at inlet temperature 60-70 C and observed LOD at 105 C for 5 minutes should not be more than 1.5 to 3% w/w.

Table6: RD parameter during drying of granules.

Parameter	Condition
Pressure	45 amp
Temp.	60-70°C
Time	Until the LOD (105°C,5 minutes) of 1.5- 3.0% w/w

Sifting

6. Discharge the granules and sift the dried granules through ASTM # 30. Collect the undersize & the over size. Pass over size dried granules through mesh ASTM # 30 using suitable milled Screen 1.0 and 0.5 mm.
7. Calculate the percent yield of granules and dispense the extra granular material accordingly.
8. Above blend and sifted extra granular Hydroxyl propyl cellulose (Klucel HXF) and Colloidal silicon dioxide through ASTM # 40 uniformly.

Blending

9. Above size granules were blending for 10 min. at 12 rpm.

Lubrication

10. Sift the Magnesium Stearate through ASTM mesh # 60 and mix with material uniformly by blending for 5 min. at 12 rpm.
11. Compress the lubricated blend into tablets using suitable punch tooling.

Layer II Sifting

1. Sift microcrystalline cellulose (PH 102), Methocel, Hypromellose K4M & API through ASTM # 20 mesh.

Dry mixing

2. Transfer the sifted mass into RMG bowl and dry mixing for 10 minutes at slow Impeller speed and chopper off.

LOD = 2.10%

BD = 0.65 gm/ml

Binder solution preparation

3. Dissolve Edetate disodium in warm water.
4. Dissolve Klucel LF and HPMC 6 Cps in purified water at room temperature.

Granulation

Table 7: granulation process parameter

Sr.no.	Process	Time (seconds)	Impelle r	Ampere s	chopper	Amperes
1	200 ml Binder addition	120	150	1.2	slow	1.2
2	Kneading	60	150	1.3	slow	1.4
3	50 ml water addition	60	150	1.2	Slow	1.2
4	Kneading	30	150	1.2	slow	1.4

Total binder addition = 200 ml Total granulation time = 4.5 min.

Drying

5. Transfer material into RD and continue the drying at inlet temperature 60-70 C and observed LOD at 105 C for 5 minutes should not be more than 1.5 to 3% w/w.

Table 8: RD parameter during drying of granules.

Parameter	Condition
Pressure	45 amp
Temp.	60-70°C
Time	Until the LOD (105°C,5 minutes) of 1.5- 3.0% w/w

Sifting

6. Discharge the granules and sift the dried granules through ASTM # 30. Collect the undersize & the over size. Pass over size dried granules through mesh ASTM # 30 using suitable milled Screen 1.0 and 0.5 mm.
7. Calculate the percent yield of granules and dispense the extra granular material accordingly.
8. Above blend and sifted extra granular Hydroxyl propyl cellulose (Klucel HXF) through ASTM # 40 uniformly.
9. Sift the FD&C Blue #2 Aluminum Lake through ASTM mesh # 60 and mix with material uniformly.

Blending

10. Above size granules were blending for 10 min. at 12 rpm.

Lubrication

11. Sift the Magnesium Stearate through ASTM mesh # 60 and mix with material uniformly by blending for 5 min. at 12 rpm.
12. Compress the lubricated blend into tablets using suitable punch tooling.

Layer III

1. Sift microcrystalline cellulose (PH 102), Sodium Starch Glycolate and adjusted quantity through ASTM # 30.
2. Magnesium Stearate through ASTM # 60 in a vibratory sifter.
3. Compress the lubricated blend into tablets using suitable punch tooling.

Compression parameters: Punch description

- Size: 8.17 mm
- Shape: Rounded
- Embossing: Upper punch-N/B Lower punch- 8/90
- Tooling : “B”

API Calculation: (g/batch)

$$\text{g/batch} = \frac{\text{Label claim X Batch size X 100}}{\text{1000 X Assay of drug as base on as is basis}}$$

Table 9: Compression details.

Sr. No	Parameters	Description
1	Appearance	Rounded, White and blue, flat uncoated tablets.
2.	Target Weight of unit tablet	680.0 mg
3.	Uniformity of Weight	680.00 mg ± 5 %
4.	Weight variation of 10 tablets	680 gm ± 5%
5.	Length	11.55 mm ± 0.2 mm
6.	Thickness	6.41 mm ± 0.2 mm
7.	Tablet breaking force	190 N to 270 N
8.	Friability (6.5 gm)	Not more than 1.0 % w/w (100 revolutions)

Table 10: Summary of general dissolution conditions.

Sr. No.	Parameter	Specifications
1.	Dissolution medium	Degassed water 900 ml
2.	Temperature	37□±2□C
3.	Rotation speed	50 rpm
4.	Volume withdrawn	10 ml
5	Apparatus	Paddle II
6	Time interval	0.5,1,1.5,2,3, 4, 6, 8hours
7.	Tablet taken	6tablet

a. Stability Studies

- Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.
- 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, light and enables recommended storage conditions, retest periods and shelf lives to be established (Natalie, 1997).

ICH specifies the length of study and storage conditions:

- Long term testing 25°C ± 2°C / 60 % RH ± 5 % for 12 months.
- Accelerated testing 40°C ±2 °C / 75 % RH ± 5 % for 6 month

4. PRE-FORMULATION RESULTS

Pre-formulation Parameters

1. API characterization results

Table 11: Analysis of API.

Test	Result	
	Bupropion	**Naltraxone**
Description	White powder	White to almost White powder
Taste and Odour	Slightly bitter & odorless	Slightly bitter & odorless
Hygroscopicity	Not hygroscopic (sample weight increased up to the 0.06% to the original weight)	Very hygroscopic
Melting point	233-234^0 c	274-276^{0}c

Sieve Analysis

Table 12: Results of sieve analysis of drug.

Sr.no.	TW (gm)	GW(gm)	PW(gm)	%R (%)	C.R (%)
#60	357.5	360.1	2.6	8.2	8.2
#80	348.7	350.7	2.0	6.3	14.5
#100	350.0	359.9	9.9	31.4	45.9
base	504.0	521.0	17.0	53.9	53.9
total	-	-	**31.5**	**99.8**	**99.8**

Flow property

The various derived properties of powder were characterized for the drug. The results were as shown in table

Table 13: Flow Property of API.

Tapped Density Test Report	Characters	
	Bupropion	**Natraxone**
Weight of material (g)	32.7 gm	29.3 gm
Initial volume (V0) in ml	72.0 ml	73 ml
Bulk Density (g/ml)	0.45 g/ml	0.40 g/ml
Tap Set Values	67 ml	70 ml
10	63 ml	67 ml
500	61 ml	64 ml
1250	57 ml	60 ml
Final volume (V1) in ml	57 ml	60 ml
Tapped Density (g/ml)	0.57 g/ml	0.48 g/ml
Carr's Index (C.I.)	20.8 %	17.80 %

Conclusion

So there was the need for wet granulation .In case of Drug the Carr's index & Hausner ratio of Bupropion is 20.8 % & 1.26 and Naltraxone is 17.80% & 1.216respectively, which indicated as drug-A& drug-B g fair to passable flow hence it was also preceded for wet granulation.

From the results of sieve analysis it was concluded that the major proportion of the API consisted of fines

Particle size distribution

Particle size distribution of Bupropion was carried out by Malvern Particle size analyzer. The results are recorded in table no. 5.4

Here, D (v, 0.1) = mean particle size of 10 % of the total particles of Drugs

D (v, 0.5) = mean particle size of 50 % of the total Particles of Drugs

D (v, 0.9) = mean particle size of 90 % of the total particles of Drugs

Table 14: Mean particle size of Drugs.

Specifications	Mean particle size of Bupropion	Mean particle size of Naltraxone
D (v, 0.1)	5.01 µm	6.13 µm
D (v, 0.5)	15.03 µm	22.42 µm
D (v, 0.9)	34.32 µm	41.23 µm

Conclusion: The results indicated that the particles of Drugs used in the studies were relatively fine.

5. Solubility Studies Solubility study of Drug

Table 15: solubility data.

Sr.no	Saturated solubility	Temp.(^{0}c)	Experimental value(mg/ml)
1	Water	26	33.3
2	Water	37	33.3
3	1.2 buffer	26	10
4	1.2 buffer	37	10
5	4.5 buffer	26	20
6	4.5 buffer	37	20
7	6.8 buffer	26	20
8	6.8 buffer	37	20
9	Ethanol	26	33.3
10	Ethanol	37	33.3
11	Acetonitrile	26	1
12	Acetonitrile	37	1

13	Methanol	26	33.3
14	Methanol	37	33.3

Table 16: Solubility data.

Sr.no	Saturated solubility	Temp.(^{0}c)	Experimental value(g/100g solvent)
1	Water	0-5	5.6
2	Water	20-25	8.3
3	Water	40-45	27.2
4	Water	80-85	>100
5	Methanol	20-25	6.6
6	Ethanol	20-25	0.9
7	2-propanol	20-25	<0.1
8	Acetonitrile	20-25	<0.1
9	Acetone	20-25	<0.1
10	Methyl acetate	20-25	<0.1
12	Ethyl acetate	20-25	<0.1

Conclusion: These drugs are water soluble according to the solubility study.

5. Drug Excipient Compatibility Study

In this study accurate weight of drug and excipient was taken as per the ratio described in compatibility protocol. It was physically mixed by trituration. Container system was 10 ml glass vial and final vials were stored at 25^{0}c/60% RH & 40^{0}C / 75% RH.

Table 17: Drug Excipients compatibility data Study of Bupropion.

Sr. No.	Drug +Excipients and ratio	Parameter	Initial Value	Condition	
				25^{0}c/60% RH	40°C+75 %RH
				1 M	1 M
01.	API	Total Impurities % API	Nil	Nil	Nil
		Appearance	√	√	√
02.	API+ Hypromellose (Methocel 6cps)	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
03.	API+L-cysteine HCl	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
04.	API+Microcrystalline Cellulose (Avicel PH 101)	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
05.	API + hydroxyl propyl cellulose (klucel HXF)	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√

06.	API + Magnesium stearate	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
07.	API + Opadry II Blue 85F90663	Total Impurities %API	√	√	√
		Appearance	Blue	Blue	Blue

Table 18: Drug Excipients compatibility data Study of Naltraxone.

Sr. No.	Drug +Excipients and ratio	Parameter	Initial Value	Condition	
				25^0c/60% RH	40°C+7 5%RH
				1 M	1 M
01.	API	Total Impurities %	Nil	Nil	Nil
		Appearance	√	√	√
02.	API+	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
03.	API+ lactose monohydrate	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
04.	API+Microcrystal line Cellulose	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
05.	API + Edetate Disodium	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
06.	API + hydroxyl propyl	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
07.	API+	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
08.	API + hydroxyl propyl	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
09.	API + HPMC K100 LVCR	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
10.	API +colloidal silicon	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
11.	API + FD&C #2 Aluminium lake	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
12.	API + Magnesium stearate	Total Impurities %API	Nil	Nil	Nil
		Appearance	√	√	√
13.	API + Opadry II Blue	Total Impurities %API	√	√	√
		Appearance	Blue	Blue	Blue

Where,

- Off white color

Excipients are considered compatible only if the total impurities do not exceed 2-times the total impurities of initial. Based on the physical and chemical data provided in above tables no significant changes observed with respect to physical appearance of the API and there was

no much increase in the impurity levels with the total obtained impurities(Known and Unknown) were within the limit . Thus, from the above we may conclude that drug is compatible with the excipients used in final formulation.

a. FORMULATION RESULT

Trial batches were carried out to develop process and standardize the formula ERtablets containing Model drugs and to minimize physical instability, assay and content uniformity problem and to match the dissolution profile as per innovator specification.

Particle size distribution

Table 19: Particle size distribution.

Sv.no.	TW (gm)	GW(gm)	PW(gm)	%R(%)	C.R(%)
#40	364.6	383.1	18.5	37.0	37.0
#60	357.5	363.1	5.6	11.2	48.2
#80	348.7	354.7	6.0	12.0	60.2
#100	350.0	359.9	9.9	19.8	80.0
Base	504.0	514.0	10	20.0	20.0
Total	-	-	**50**	**100**	**100**

Physical parameter of blend and tablet

Table 20: Physical parameter of blend

Sr.no.	LOD		BD		TD		CI		HR	
	A	B	A	B	A	B	A	B	A	B
T1	1.8	1.6	0.310	0.63	0.42	0.78	26.19	19.56	1.35	1.243
T2	1.9	1.9	0.350	0.52	0.410	0.52	14.63	25.64	1.17	1.345
T3	2.2	2.5	0.330	0.50	0.39	0.67	15.38	25.0	1.18	1.333
T4	2.0	2.1	0.356	0.53	0.472	0.64	25.53	16.07	1.25	1.191
T5	2.1	2.3	0.46	0.54	0.54	0.67	14.81	19.56	1.17	1.243
T6	1.9	1.9	0.46	0.49	0.55	0.67	16.36	27.45	1.19	1.378
T7	2.0	2.1	0.44	0.53	0.53	0.64	16.98	16.01	1.20	1.193
T8	2.0	2.2	0.46	0.55	0.54	0.73	14.81	24.32	1.17	1.321

Physical (Core Tablet) parameter of process development batches

Table 21: Physical (Core Tablet) parameter of process development batches.

Batch No.	Average wt.(mg)	Thickness (mm)	Diameter (mm)	Hardness (N)	Friability (% w/w)	Assay
T1	684.7	6.27	12.01	225	0.32	90.4
T2	675.6	6.31	11.99	232	0.25	99.98
T3	693.4	6.26	12.02	236	0.36	99.74
T4	672.1	6.26	12.01	225	0.51	99.50
T5	678.4	6.30	12.00	229	0.60	99.99
T6	683.6	6.28	11.99	235	0.52	99.18
T7	679.6	6.29	12.01	238	0.42	99.89

T8	677.9	6.30	12.02	234	0.53	99.81

In-vitro Dissolution release of different formulation batches

Table 22: In-vitro Dissolution release of different formulation batches.

Sr. no.	Time(hrs)	Innovator		Formulation batches from T1 to T4							
				T1		T2		T3		T4	
		A	B	A	B	A	B	A	B	A	B
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0.5	24	35	22	24	25	23	35	26	22	33
3	1	37	53	34	37	40	38	42	34	33	53
4	1.5	46	66	41	46	49	50	55	46	41	66
5	2	54	76	49	55	57	62	64	58	47	75
6	3	65	86	60	68	68	78	71	65	58	87
7	4	73	92	68	78	76	89	80	76	65	94
8	6	83	96	81	92	86	99	91	89	78	97
9	8	89	99	90	100	92	104	95	95	86	98

Table 23: F1-F2 factor results for T1 – T4.

	Acceptance criteria	T1		T2		T3		T4	
		A	B	A	B	A	B	A	B
Similarity Factor	50 -100	63	34	69	41	47	33	55	75
Dissimilarity Factor	0 – 15	6	17	5	13	13	19	9	2

Table 24: In-vitro Dissolution release of different formulation batches

Sr.no.	Time(hrs)	Innovator		Formulation batches from T5 to T8							
				T5		T6		T7		T8	
		A	B	A	B	A	B	A	B	A	B
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0.5	24	35	23	33	22	22	21	33	24	33
3	1	37	53	43	53	33	33	37	53	37	52
4	1.5	46	66	58	65	41	41	48	67	44	66
5	2	54	76	69	75	47	47	57	72	54	75
6	3	65	86	86	85	58	58	70	85	63	86
7	4	73	92	89	96	65	65	79	94	71	94
8	6	83	96	96	99	78	78	89	99	84	98
9	8	89	99	99	103	86	86	94	104	89	103

Table 25 F1-F2 factor results for T4 – T8.

	Acceptance criteria	T5		T6		T7		T8	
		A	B	A	B	A	B	A	B
Similarity Factor	50 -100	37	72	55	25	61	70	84	77
Dissimilarity Factor	0 – 15	20	3	9	29	6	3	1	2

Conclusion

From the above dissolution results are concluded that T4 & T8 formulation batches of

dissolution release are similar to innovator product.

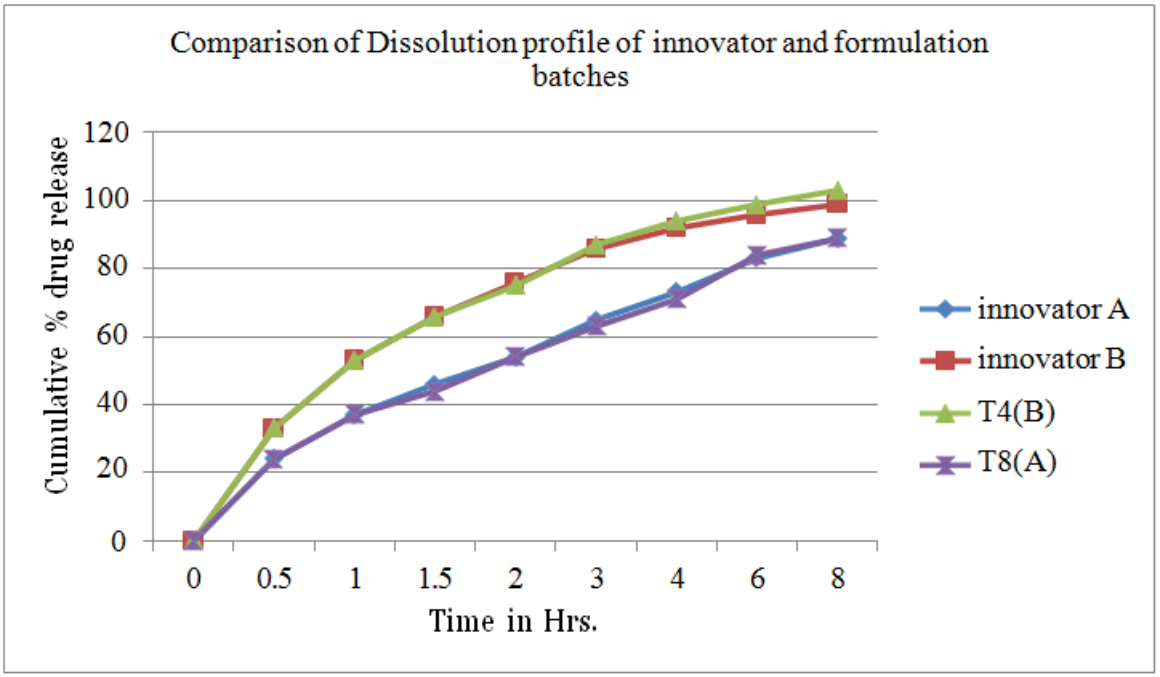

Fig. 8:1 Dissolution profile of innovator and formulation batches (T4& T8).

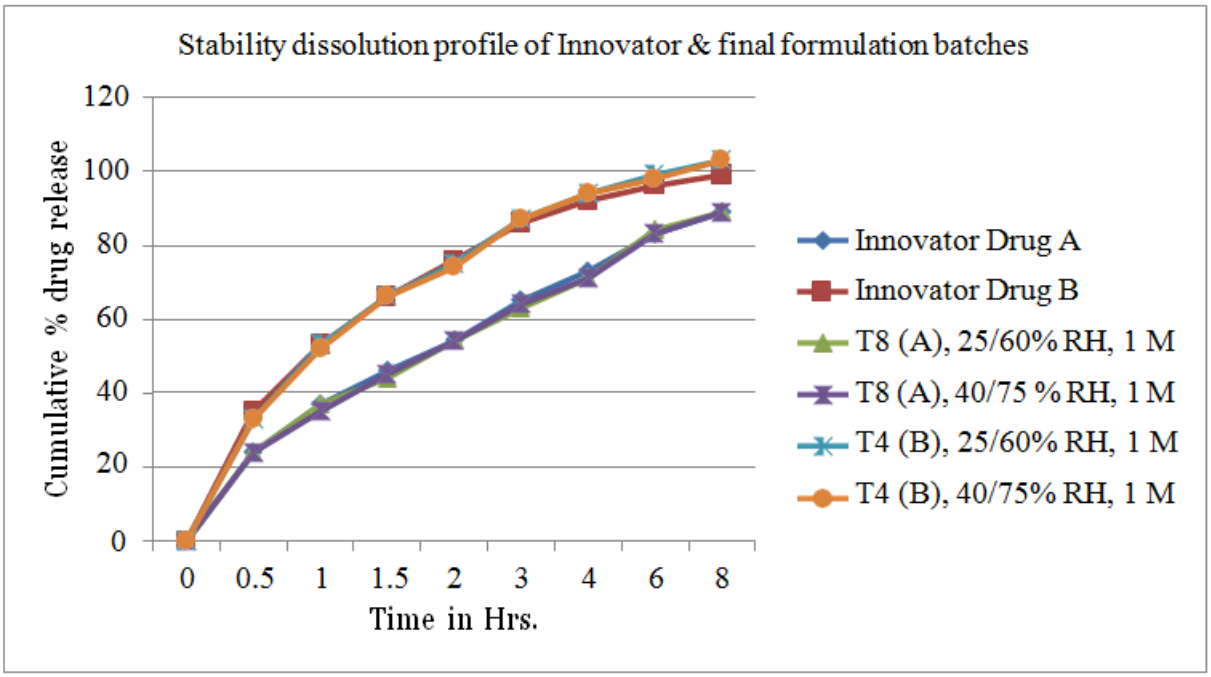

Fig. 8.2: Stability dissolution profile of innovator and formulation batches.

b. Comparison of dissolution data of formulation batches (coated tablets) with innovator (Degassed water)

Table 26: Dissolution Profile.

Sr. no.	Time (in hrs)	Innovator		Formulation batches	
		A	B	(T8) A	(T4) B
1	0.00	0.00	0.00	0.00	0.00
2	0.5	24	35	24	33
3	1.0	37	53	37	53
4	1.5	46	66	44	66
5	2.0	54	76	54	75
6	3.0	65	86	63	87
7	4.0	73	92	71	94
8	6.0	83	96	84	97
F2	8.0	89	99	89	98

Conclusion: From the dissolution data comparison as shown in table optimized batches matched with the innovator dissolution profile.

c. Stability study of batch T8

Table 27: Stability observations of batch T8.

Storage condition	**Room Temperature**		**1Month**				**Limitation**
Period	**Initial**		**25ºC/60% RH**		**40ºC/75%RH**		
Formulation	T8		T8		T8		
Parameters	**A**	**B**	**A**	**B**	**A**	**B**	
Physical Appearance	Oval white	Oval blue	Oval white	Oval blue	Oval white	Oval blue	No change should observed
Highest unknown Impurity (%)	0.042	0.044	0.052	0.054	0.156	0.158	NMT 0.2%
Highest Known Impurity (%)	0.024	0.027	0.042	0.045	0.675	0.700	NMT 0.5%
Total Impurity (%)	0.093	-	0.095		0.126	-	NMT 2%
Assay	99%	98%	98.8%	99%	98.7%	99%	-

CONCLUSION

Stability study of Optimized batch T10 was kept on stability condition 40°C/75 % RH for 1 month, Initial at room temperature and tablets were observed for any physical change then it was found that there was no change in the color and appearance. Also results of the stability studies concluded that there was no any significant change in the drug release and lag time of drug in pH 6.8 phosphate buffer, and impurity level in tablets were within the specified limit as shown in table when stored at 40°C, 75 %RH, for period of 1 month. Hence it may be concluded that optimized batch T8 tablets were stable.

Table28: Stability dissolution profile of batch T8.

Time (Hrs)	Innovator		T8 of drug-bupropion 25ºC/60%RH	T8 of drug-bupropion 40ºC/75%RH	T4 of drug-Naltraxone B25ºC/60%RH	T4 of drug-Naltraxone 40ºC/75%RH
	A	B	1 Month	1 Month	1 Month	1 Month
0	0.0	0.0	0.0	0.0	0.0	0.0
0.5	24	35	24	24	33	33
1	37	53	37	35	53	52
1.5	46	66	44	45	66	66
2	54	76	54	54	75	74
3	65	86	63	64	87	87
4	73	92	71	71	94	94
6	83	96	84	83	99	98
8	89	99	89	89	103	103

Physical parameters innovator tablet and formulation tablet

Table 29: Physical parameters innovator tablet and formulation tablet.

Sr. No.	Tests	Innovators tablet	Formulated tablets
1	Average weight (mg)	684.00	684.7
2	Thickness (mm)	6.30	6.29
3	Diameter (mm)	12.0	12.01
4	Friability (%)	0.32	0.32
5	Hardness (N)	220	221

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