WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 18, 1277-1290. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF NITROFURANTOIN BI-LAYER TABLET

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Article Received on
11 September 2018,

Revised on 02 October 2018,
Accepted on 23 Oct. 2018,

DOI: 10.20959/wjpr201818-13648

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ABSTRACT

Nitrofurantoin (NFT) is an antibacterial drug. Nitrofurantoin is slightly soluble in water. Nitrofurantoin shows both bacteriostatic and bactericidal effects. Bacteriostatic or bactericidal effect inhibits the synthesis of DNA, RNA, protein and cell wall synthesis. The sustained release tablet will optimize safety of a drug and therapeutic effect. Main aim to prepare sustained release tablet is patient convenience and compliance. The study deals with Nitrofurantoin (NFT) bi-layer tablet. This helps in reducing frequent dosing and to overcome patient compliance. The bi-layer tablet contains immediate release and sustained release layer. To prolong the effect of dug release by adding control releasing agent i.e, Carbopol71G.The optimized batch shows the 98% release in 8 hrs. In batch T5 the release was very fast as required to maintain the release up to 8 hrs. X-ray diffraction (XRD), Differential scanning calorimetry (DSC), Fourier Transform Infrared (FTIR) spectra study was carried out.

KEYWORDS: Nitrofunrantoin, Bilayer tablet, Dry mix, X-ray diffraction, Differential scanning calorimetry, Fourier Transform infrared (FTIR).

INTRODUCTION

Oral route is widely accepted as it provides huge range of advantages as patient compliance, ease of administration and dose modification. Conventional dosage forms are modified to provide sustained release and/or better therapeutic success by using suspension, capsule, matrix tablet formulations, mouth dissolving formulations etc. Sustain release formulation is an important program for new drug research and development to meet several clinical needs.

Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release in one layer as maintenance dose and immediate release of second layer as initial dose of same drug. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles.

Several pharmaceutical companies are currently developing bi-layer tablets. For a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets.

Uncomplicated UTIs Nitrofurantoin is not recommended for the treatment of pyelonephritis,[14] prostatitis,[15] and intra-abdominal abscess,[16] because of extremely poor tissue penetration and low blood levels. Nitrofurantoin is pregnancy category B.[7] It is one of the few drugs commonly used in pregnancy to treat UTIs.
Nitrofurantoin is available in two forms;
1. Nitrofurantoin macrocrystal
2. Nitrofurantoin monohydrate.

The present study is an attempt to use both these forms in following manner:
The proposed bilayer tablet contains the Nitrofurantoin macrocrystal as first layer (IR) in the dose of 75mg. Nitrofurantoin macrocrystal is having more solubility and rapid dissolution. It is more stable form in comparison with Nitrofurantoin monohydrate.

The Nitrofurantoin monohydrate is proposed to be second layer (SR) with the dose of 25mg.

Nitrofurantoin monohydrate is less soluble, stable in comparison with Nitrofurantoin macrocrystal.

The proposed study is intended to develop a bilayer tablet of Nitrofurantoin which provides the drug release up to 8-10 hrs. with better patient compliance.

MATERIALS AND METHODS

Nitrofurantoin was obtained from Unimarck Chemicals Ltd. Mumbai. Lactose monohydrate, Pregelatinized starch 1500 Loba chemicals, Colloidal silicon Dioxide Aerosil 20, Purified

Talc, Povidone(Kollidone30) VijilakpharmaLtd.Mumbai, Carbopol 71G Lubrizol chemicals, Magnesium Stearate SD Fine chem Ltd. Mumbai.

Preparation of Bi-layer tablet:

- Formulation of Immediate release layer: Dry Mixing
- Formulation of Sustained release layer: Dry Mixing
- Direct compression technique.

Preparation of Step I: Immediate release layer

1. Take Lactose monohydrate SD 11, Starch 1500, Talc was cosifted through # 30 ASTM.
2. Aerosil 200 was sifted through #60 ASTM.
3. Nitrofurantoin Macrocrystal was sifted through # 20 ASTM
4. All cosifted excipients and API was blended for 15 min at 9 RPM.
5. Magnesium stearate sifted through #30 ASTM and blended with above blend for 5 min.

Preparation of Step II: Sustained release layer

1. Take Nitrofurantoin monohydrate, Lactose monohydrate SD 11, Carbopol 71 G, Talc and cosifted through # 20 ASTM.
2. Povidone K30 was sifted through #30 sifted
3. Aerosil 200 was sifted through #60 ASTM.
4. All cosifted excipients and API was blended for 15 min at 9 RPM.
5. Magnesium stearate sifted through # 30 ASTM and blended with above blend for 5 min.

Step III

1. Compression of Bilayer tablet of layer I (Immediate release) and layer II (sustained release) by using Cadmach tablet compression machine.

Table 1: Composition of different formulation.

Sr. No.	Ingredients	BT1	BT2	BT3	BT4	BT5	BT6	BT7	BT8	BT9
	Layer I									
1	Nitrofurantoin macrocrystal	25	25	25	25	25	25	25	25	25
2	Lactose SD 11	60	60	50	60	50	60	50	60	60
3	Starch 1500	13	12.5	13	13	50	15	18.5	13	50
4	Aerosil 200	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
5	Talc	1	1	1	1	1	1	1	1	1
6	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	Layer II									
1	Nitrofurantoin	81	81	81	81	81	81	81	81	81

	monohydrate									
2	Lactose SD 11	40	40	40	40	40	40	40	40	40
3	Povidone K30	25.55	32.5	57	25.55	46	52.5	32.5	25.5	42
4	Aerosil 200	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
5	Carbopol 71 G	9.5	32.5	8	39.45	19	12.5	8.5	28.6	8
6	Talc	3	3	3	3	3	3	3	3	3
7	Magnesium stearate	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8

Characterization of Bi-Layer Tablet

Characterization of the tablet is done by taking;

Shape, Colour, Weight variation, Hardness, Thickness, Dissolution, Assay.

Melting Point By Melting Point Apparatus

The melting point of drug was determined by capillary rise method and compared, whether it complies with the reported ones.

Differential Scanning Calorimetry (DSC)

The thermal behaviour of drug was determined using Mettler Toledo differential scanning calorimeter. Samples were placed in aluminum crucible and the DSC thermograms were recorded at heating rate of 10^0 C/ min in the range 20 to 300^0C under nitrogen atmosphere.

Powder X-Ray Diffraction (XRD)

The powder X-ray diffraction (PXRD) patterns were recorded by X-ray diffractometer model number D8 (Advance Brucker AXS). A focused graphite monochromater equipped after the sample was used for employing Cu Kα radiation (λ = 1.5405Å). Samples were scanned from 10^0 to 80^0.

Fourier Transform Infrared (FT-IR) SPECTROSCOPY STUDY

FTIR study was carried out to identify API. The samples were scanned in the range of 400 to 4000 $cm^{-1.}$

Drug- Excipients Compatibility Study

The primary objective of this study was to identify a stable storage condition for drug in solid state and identification of compatible excipients for its formulation. A stable and effective dosage form depends on the careful selection of excipients that are added in the formulation. Three sets of each mixture are prepared, from which 1 set is for initial analysis while two sets are kept at 40ºC / 75 % RH for 1 month by using open glass vials and closed glass vials for any physical change (26). Compatibility of drug with different excipients was done using

open glass vials and closed glass vials at specific storage conditions and checked at various time intervals for any physical change. The powder mix in the vials was observed for any physical change compared to its initial property.

Table 2: Compatibility conditions.

Sr. No.	Condition	Time-point	Type of packing
1	Initial	Zero day	Glass vial
2	40^{o}C/ 75% RH	Up to 30 days	Glass vial

IPQC Tests for Powder Blend

Density

Bulk density, Tapped density, Hausner's ratio, and Compressibility index were calculated by using tap density apparatus.

Loss on drying

LOD was calculated by using Halogen moisture balance analyzer. Sample was kept for 15 min at 105^{0}c.

IPQC Tests for Tablets

Descriptions

Compressed Bilayer tablets were pale yellow in color, round shaped, and uncoated tablets.

Tablet thickness

Tablet thickness is important for tablet packaging, very thick tablet affect packaging either in blisters or in plastic containers. Tablet thickness is determined by the diameter of die, the amount of fill permitted to enter die and force or pressure of applied during compression. Thickness of tablets was measured by manually by using Vernier caliper. The thickness should be controlled with in $\pm$5% variation of standard value.

Hardness and friability test

The tablet should show sufficient mechanical strength to withstand fracture and erosion during manufacturing and handling. Hardness test and friability test used to check mechanical strength.

Hardness

Dr. Schleuniger hardness tester was used to check hardness of tablet.

Friability test

Tablets that tend to power, chip and fragment when handled, lack elegance and consumer acceptance. It also creates excessively dirty process in areas of manufacture such as coating and packaging. This leads to weight variation and content uniformity problem in tablets. The laboratory friability tester is known as the Roche friabilator. This device subjects a number of tablets should not loss more than 1% of their weight to be acceptable.

Weight variation test

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in table and none deviate by more than twice the percentage shown in.

Table 3: Weight variation.

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10.0
130-324	7.5
More than 324	5.0

Table 4: Characteristics of bilayer tablet.

Sr. No.	Parameter	Observation
1	Shape	Round
2	Colour	Yellow
3	Average Weight	294
4	Average Hardness (kp)	10-11.5
5	Average Thickness (mm)	3.20-3.40
6	Friability %	Nil

Stability Studies

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of label potency and its physical characteristics have not changed appreciably or deleteriously.

RESULTS AND DISCUSSION

The bi-layer tablet was successfully prepared by using polymers such as Carbopol and PVP. The prepared bi-layer tablets were evaluated for various evaluation parameters like Shape, Color, Weight variation, Hardness, Thickness, Dissolution, Assay.

Table 5: Tests for tablets of batches F1 to F9.

Parameter	**Observations**								
Batch	**BT1**	**BT2**	**BT3**	**BT4**	**BT5**	**BT6**	**BT 7**	**BT 8**	**BT 9**
Average Weight (mg)	293	294	294	295	294	295	294	294	295
Average Hardness (Kp)	8	10	10	11.5	11.1	12.1	10.5	11	11.5
Average Thickness (mm)	3.33	3.44	3.47	3.47	3.42	3.49	3.20	3.25	3.51
Friability (%)	0.095	0.16	0.092	0.18	0.12	0.092	0.09	0.015	0.014
Loss on drying (%)	1.5	1.6	1.4	1.3	1.1	1.3	1.2	1.4	1.5

Differential Scanning Calorimetry (DSC)

The thermal behaviour of drug was determined using Mettler Toledo differential scanning calorimeter. Samples were placed in aluminum crucible and the DSC thermograms were recorded at heating rate of 10^0 C/ min in the range 20 to 300^0C under nitrogen atmosphere.

The above Differential scanning calorimetry graphs of Nitrofurantoin macrocrystal and Nitrofurantoin monohydrate shows the sharp peak. The above peaks are exothermic.

DSC Graph

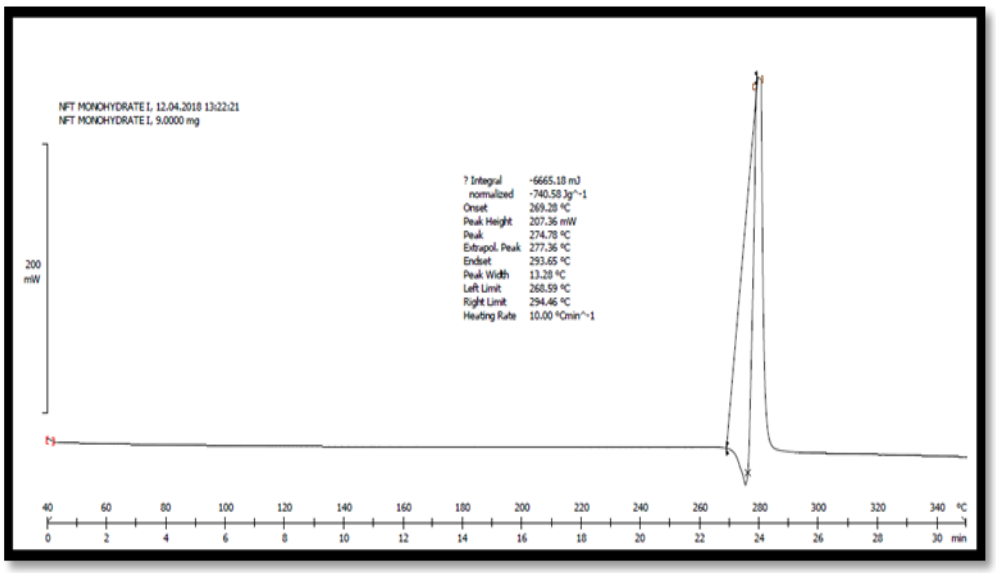

Fig 1: Nitrofurantoin monohydrate.

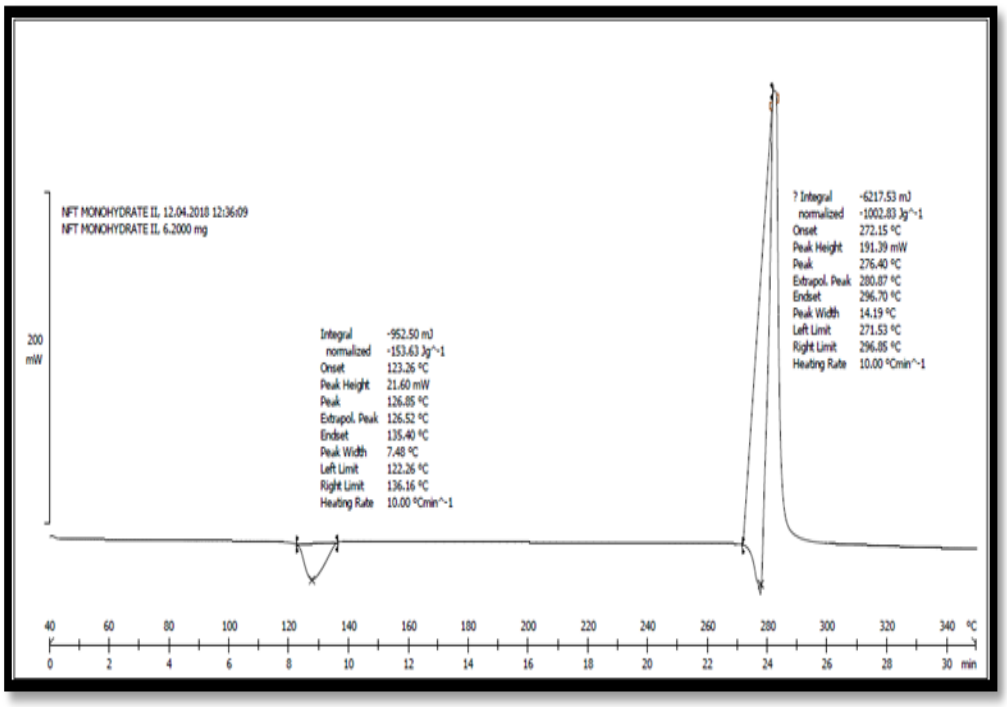

Fig. 2: Nitrofurantoin macrocrystal.

Fourier Transform Infrared (FT-IR) Spectroscopy Study

FTIR study was carried out to identify API. The samples were scanned in the range of 400 to 4000 $cm^{-1.}$

The above given graphs are of Nitrofurantoin macrocrystal, Nitrofurantoin monohydrate. It shows the absorbance at 266 NM.

FT-IR Analysis

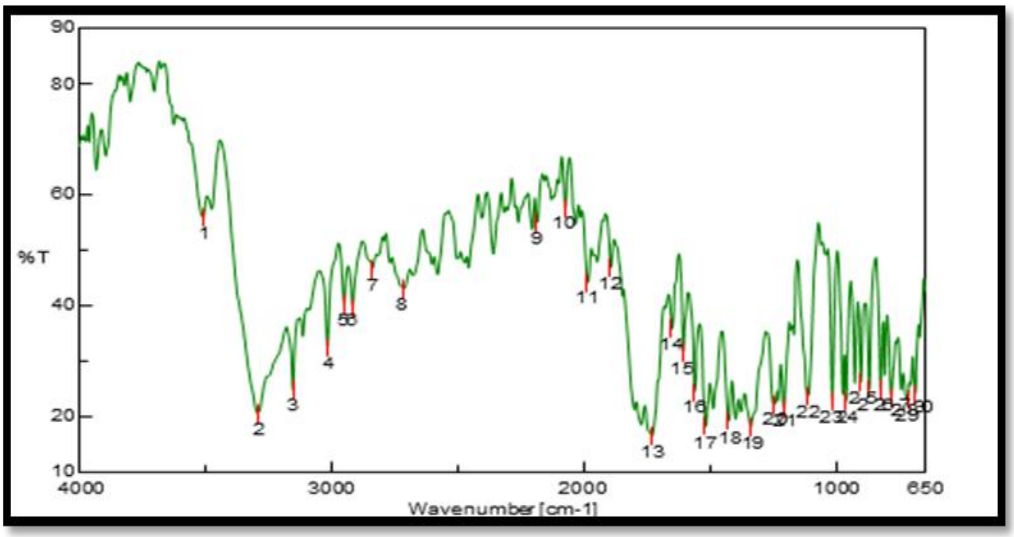

Fig. 3: Nitrofurantoin macrocrystal.

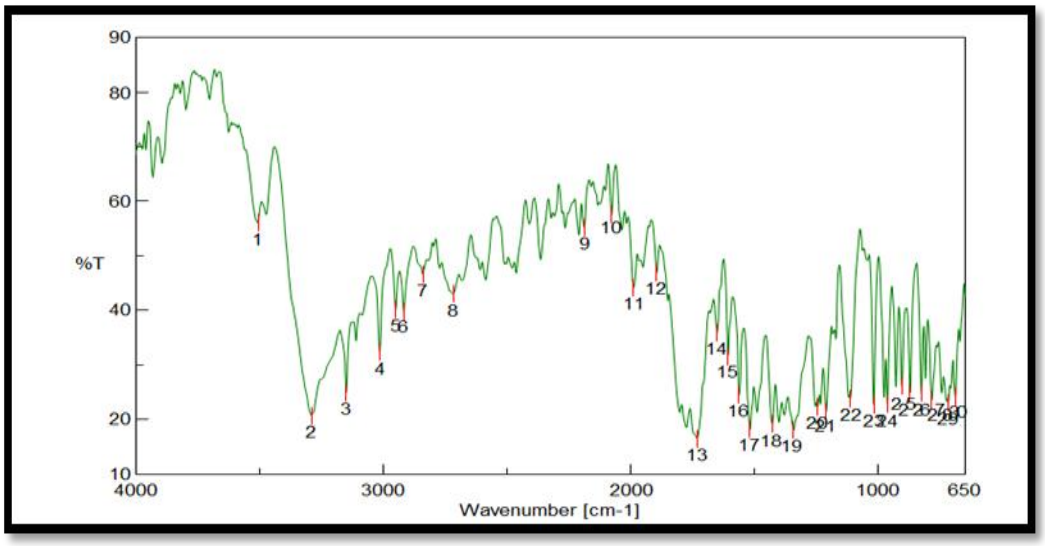

Fig. 4: Nitrofurantoin monohydrate.

X-Ray Diffraction Study (XRD)

X-ray diffractograms of initial formulation and formulation after one month. Hence XRD was carried out to study any polymorphic change in formulation after one month stability study.

The crystallinity of formulation was evaluated by using Philips diffractometer and Cu- Ka line as a source of radiation which was operated at the voltage 40kV and current 30mA. The samples were measured in the 2θ angle range between 20º and 60º.

The XRD study shows the non identified peaks for amorphous substance and the crystalline substance shows the sharp peaks.

XRD Study

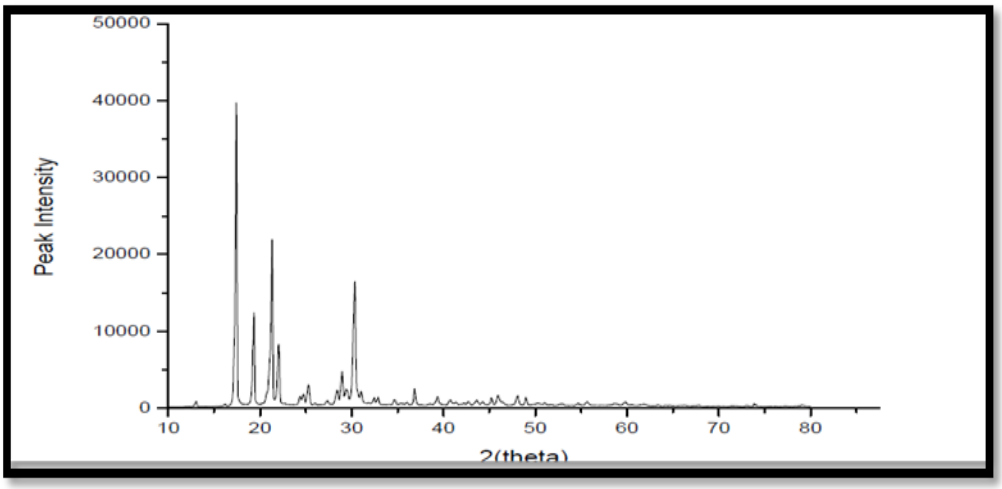

Fig. 5: Nitrofurantoin macrocrystal XRD.

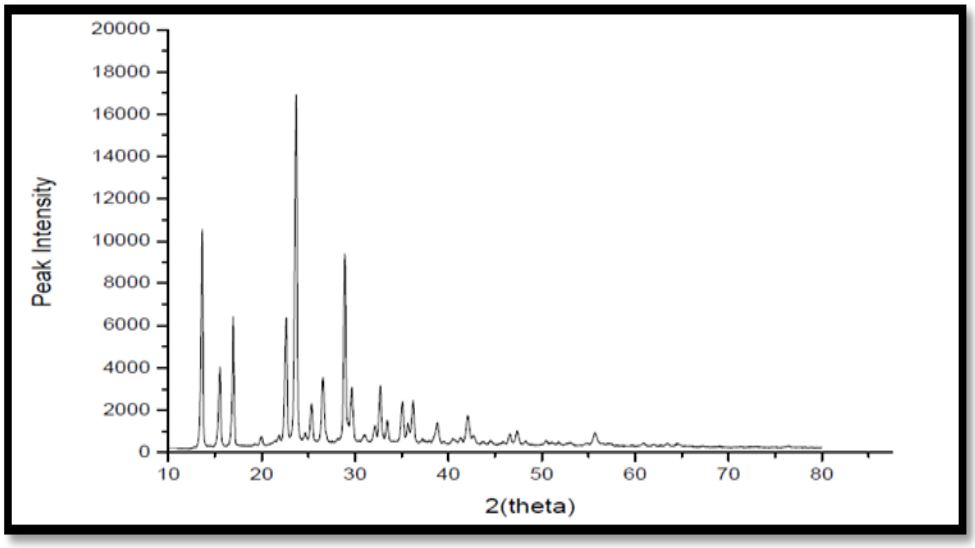

Fig. 6: Nitrofurantoin monohydrate.

Drug- Excipients Compatibility Study

The primary objective of this study was to identify a stable storage condition for drug in solid state and identification of compatible excipients for its formulation. Three sets of each mixture are prepared, from which 1 set is for initial analysis while two sets are kept at 40ºC / 75% RH for 1 month by using open glass vials and closed glass vials for any physical change. Compatibility of drug with different excipients was done using open glass vials and closed glass vials at specific storage conditions and checked at various time intervals for any physical change. The powder mix in the vials was observed for any physical change compared to its initial property.

This study shows the incompatibilities between drug and excipients. The composition ratio of drug and excipient is 1:1. After one month there is no color change occurs that means there is no incompatibility between the drug and excipients.

Table 7: Composition for Drug- Excipient compatibility study.

Sr. No.	Physical admixture	Drug: Excipient	Initial description
1.	API	1	Yellow colour powder
2.	API + Lactose monohydrate	1:1	Yellow colour powder
3.	API + Starch 1500	1:1	Yellow colour powder
4.	API + Aerosil 200	1:1	Yellow colour powder
5.	API + Povidone K30	1:1	Yellow colour powder
6.	API + Carbopol 71 G	1:1	Yellow colour powder
7.	API + Magnesium stearate	1:1	Yellow colour powder

Drug Release

All the 9 batches of prepared bilayer tablet show the different drug release profiles. From the all batches BT7 shows the good drug release. So comparison of Prepared batch and marketed formulation was studied.

Table 8: Comparison of Release rate of Batch T7 & Marketed formulation.

Batch Descriptions	BT7	Marketed formulation
0	0	0
15	19	23
30	26	27
45	31	30
60	41	33
120	49	40
180	53	48
240	60	53
300	69	61
360	80	67
420	89	70
480	98	72
Assay	99.2	76.1

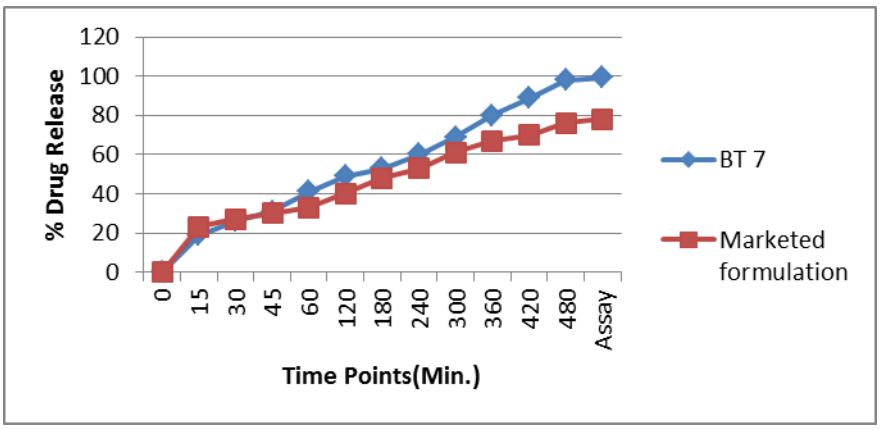

Fig. 7: Comparison of prepared bilayer tablet and Marketed formulation.

Dissolution Study

Apparatus : USP Type II (Paddle)

Dissolution medium : pH 7.4 buffer medium

Dissolution volume : 900mL

Speed : 100rpm

Temperature : 37.0± 0.5ºC

Time intervals : 1,2,3,4,5,6,7, 8hrs

The dissolution study was performed by using above parameters. The different batches show the different drug release.

Table 9: Dissolution profile.

Formulation's	Drug Release											
Time(Min)	**0**	**15**	**30**	**45**	**60**	**120**	**180**	**240**	**300**	**360**	**420**	**480**
BT1	0	21	29	34	39	50	58	68	79	88	92	92
BT2	0	23	26	32	36	46	67	76	81	87	93	94
BT3	0	26	30	36	41	55	69	78	80	85	90	91
BT4	0	22	26	35	41	50	59	64	71	82	89	94
BT5	0	23	28	33	39	47	55	59	67	76	85	96
BT6	0	21	24	31	45	51	57	62	72	80	88	95
BT7	0	19	26	31	41	49	53	60	69	80	89	98
BT8	0	20	24	32	38	48	54	62	70	79	86	94
BT9	0	22	26	35	36	51	58	66	75	82	90	93
Marketed Formulation	0	23	27	30	33	40	48	53	61	67	70	76

Stability Studies

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of label potency and its physical characteristics have not changed appreciably or deleteriously.

Table 10: Stability data at 40°C/75% RH.

Tests	**Specifications**	**Initial**	**1month** **40°C/75%RH**
Description	Yellow, uncoated, round, biconvex tablets, plain on both sides	Yellow, uncoated, round, biconvex tablets, plain on both sides	Yellow, uncoated, round, biconvex tablets, plain on both sides
Thickness	For information	3.30 mm	3.31mm
Hardness	For information	4.4 kp	4.3 kp
Uniformity of weight	294±10% (285mg to 304 mg)	294 mg	294.5mg
Assay	NLT 90% and NMT110% of labeled amount of drug	99.5%	99%
Related Sub.	**a) Any unknown impurity NMT 0.20% ww** b) Total impurity NMT 1%w/w	Not detected	Not detected
% Release rate (Medium/App)		99% Release	102 % Release

*NA - not applicable

Observation: From above data it was concluded that sample passes stability at 40°C/75%RH condition.

CONCLUSION

Pharmaceutical have made a major contribution improving the health status of patients over a past few decades. Tablet is defined as a compress solid dosage form containing medicament without excipients. Bi-layer tablets offer an excellent opportunity for manufacturers to separate themselves from their competitors, improve their product's efficacy, and protect against impersonator products. Bi-layer tablets consist of two layer which is immediate release and sustained release layer. The immediate release layer is proposed with the aim of reaching a high serum concentration in a short period of time, the second layer is controlling release which is designed to maintain an effective plasma level for a prolonged period of time. The design of oral sustain drug delivery system (SDDS) should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. The average thickness of tablet is 3.47 and drug release is 98% in 8 hrs. %. Accelerated stability study was performed in this project work. The accelerated stability study showed that there were no significant changes in weight, thickness.

ACKNOWLEDGEMENTS

The gift sample taken from TEVA Pharmaceuticals Ltd, Ambarnath, Mumbai.

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