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FORMULATION AND EVALUATION OF TOLMETIN SODIUM COX-2 INHIBITORS FOR TREATMENT OF OSTEOARTHRITIS

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ABSTRACT

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. Bi- layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The main objective of my research work is to develop a bilayer tablet of Tolmatine sodium, in which one layer is immediate layer for immediate action and second layer is the sustain release layer for maintaining the dose of the drug.

KEYWORDS: Tolmetin Sodium, COX-2 Inhibitors, Osteoarthritis.

INTRODUCTION

Oral route has been the most widely used and most convenient route for the drug delivery. Oral route of administration has received more attention in the pharmaceutical industry and research field because of the flexibility in designing of dosage form and constraints like

sterility and potential damage at the site of administration.[1]

Approximately 50% of the drug delivery system available in the market is oral drug delivery system which has more advantages due to patient acceptance and easy to administration. The oral absorption of drug is often limited due to short GRT i.e. the time required for the content of the stomach to enter into smallintestine.[2]

All the pharmaceutical formulation for systemic effect via oral administration must be developed within intrinsic characteristics of gastrointestinal physiology. The needs of GIT physiology, Pharmacodynamics, pharmacokinetics &formulation design is essential to achieve a systemic approach to the successful development of an oral formulation dosage form. The scientific framework required for the successful development of an oral drug delivery system consists of basic understanding of the following threeaspects:

- Physicochemical, pharmacokinetic & pharmacodynamic of thedrug.
- The Anatomical and physiological characteristics of GIT.
- Physicochemical characteristics & drug delivery system and type of dosage formdesign.[3]

1.1 Tablet

Tablet defined as solid pharmaceutical dosage form containing drug substance with or without suitable diluents and prepared by either compression or molding method. They have been in wide spread use since the later part of the 19th century and they are popularity continue.[4]

1.1.1 Advantages of tablet

1. Accuracy of dosage and ease ofadministration.
2. They are better suited to large scale production then other unit oralformulation.
3. They have chemical, mechanical and microbiological stability of all the oral formulation.

EXPERIMANTALMETHOD

Preformulation Methods is defined as testing of physical and chemical properties of a drug substance with and without excipient. The objective of preformulation testing is to develop stable and bioavailable dosage form.

The biological and analytical requirements needed for the registration of an active pharmaceutical ingredient (API), whether of natural or synthetic origin are the focus of much

attention in the pharmaceutical industry. The ever increasing requirements with regard to ensuring safety, quality, efficacy has meant that the development of new medicines is characterized by higher assay values and lower impurity content. However, the quality of a dosage form does not depend only on the characteristics of the active substance but also on the excipients used to manufacture the dosage form and many stability problems seen in development of dosage forms are due to incorrect matching of excipients and an API.

5.1 Physical Description

5.1.1 Organoleptic properties

5.1.1.1 Odour

Very less quantity of drug was taken and smelled for determination of its odour.

Table 5.1: Physical Properties of Tolmatine Sodium.

Test	Standard	Observation
Colour	White crystalline	White
Odour	Odour less	Odour less
Taste	Bitter	Bitter

5.2. Solubility Analysis

A Qualitative determination was done by adding a solvent to a fixed amount of solute to a test tube.

Procedure: By adding a solvent to a fixed amount of solute to a test tube. After each addition test tube was shaken and visually observed. Solubility Profile of Tolmatine sodium in various solvents are shown in Table.

Table 5.2: Solubility profile of drug.

S. No.	solvent	Solubility
1	Water	Sparingly soluble
2	Phosphate buffer 5.8	Soluble
3	methanol	Soluble
4	0.1 N HCl	Soluble

5.3 MELTINGPOINT

Melting Point

It is one of the methods to check the purity of crude drugs. In pure chemicals or photochemical, melting points are very sharp and constant. Since the crude drugs contain the multiple of chemicals which have fixed range of melting point.

Procedure: Capillary Method

Table 5.3: Melting point of drug.

Drug	Specified	Observations
Tolmatine sodium	210^0C	207^0C

5.4 IDENTIFICATION OF DRUG BY INFRAREDSPECTROSCOPY

Infrared spectroscopy is widely used analytical technique which provides information about the structure of molecule. Infrared spectrum of chemical substances is fingerprint for its identification. An infrared spectrum of drug was taken using KBr pellets. Small quantity of drug was mixed with oil and one drop was placed between KBr pellets. The pellets were in holder and infrared spectrum was interpreted for presence of different group in the structure of drug. The Fourier transform infrared spectra of showed Tolmatine sodium all characteristic peaks of Tolmatine sodium.

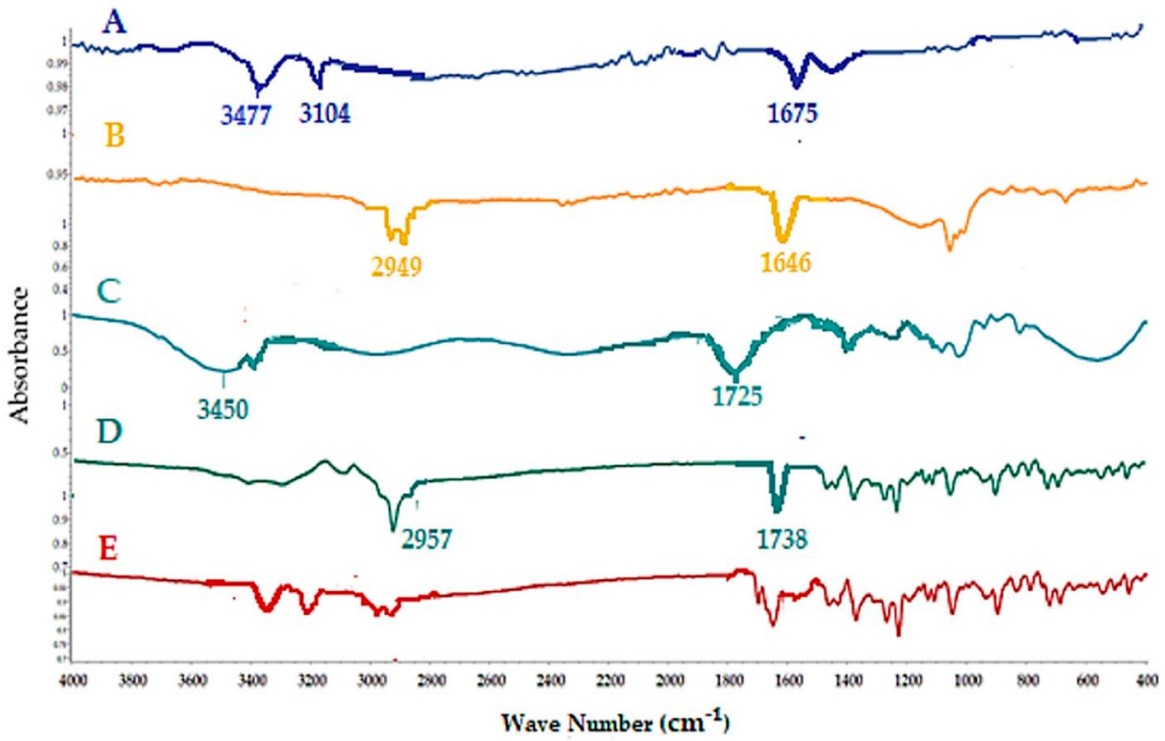


Figure No. 5.4.1 FTIR spectra of drug and excipient.

Tolmetin (A), Crosspovidone (B), Hydroxy propyl methyl cellulose (C), Microcrystalline cellulose (D), Magnesium stearate (E)

Table 5.4: Infra red characteristics of Tolmatine sodium drug sample.

S. No.	Wave no.(cm^{-1})	Interpretations
1.	1588.60	Ketone carbonyl (C=O) Group
2.	1675.48	Carbonyl group of carboxylic acid
3.	1750	Methylene Group
4.	3104.03	C-H Stretching Vibration

5.5 IDENTIFICATION OF DRUG BY ULTRA VIOLET SPECTROSCOPY

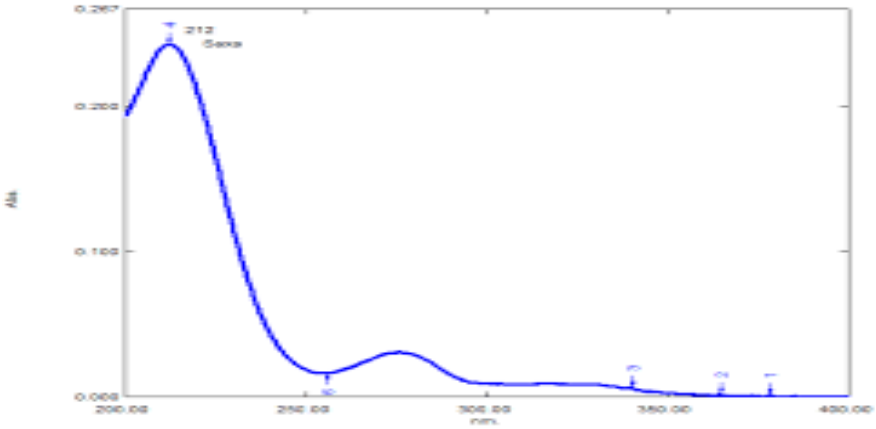


Figure No. 5.5: UV spectra of the sample drug.

5.6 ANGLE OFREPOSE

It is explained as the maximum angle between the pile height of the powder and the half of the pile diameter.

Procedure: Funnel method was applied. A funnel was attached with its tip at certain height (h), above the horizontal surface were graph paper was kept. Powder was passed from the funnel until the tip of pile touches the funnel andcalculated.

$\theta = tan\text{-}1(h/r)$

Table no 5.8 Angle of Repose Guidelines.

Angle of Repose (in degrees)	Type of flow
<25	Excellent
25-30	Good
30-40	Poor
>40	Very poor

5.7 CARR' SINDEX

Carr's Index (CI) which provides an indication of the compressing strength of a powder and therefore the potential for use as a suitable tablet formulation component. The CI guidelines are.

6. RESULTS AND DISCUSSION

Formulation

The controlled release limited by solubility was precluded and delivery of active material form the preparation was controlled by the formulation. All formulation were prepared in bilayer foam in which first layer is 'immediate release layer' consist of Crosspovidone which is super disintegrate which provide fast release of active material and the second layer 'sustained release layer' consist of HPMC provided controlled release of active material. In the present study, hydrodynamically balanced systems of Tolmatine sodium were prepared by.

Table 6.1: Hardness test of bilayer tablet.

Parameter	Observation (Kg/cm^2)
Hardness	7.3±0.19

Where all values are mean ± S.D. for n=3

Table 6.2: Friability of bilayer tablet.

Parameter	Observation	Reference
% Friability	0.74±0.059	Not more than 1%

Where all values are mean ± S.D. for n=3

Preformulation study was performed and the results were directed for the further course of formulation. Organoleptic properties study i.e., solubility study, identification and Authentification of drug, and quantitative estimation of drug and compatibility study were carried out during preformulation study. These tests were performed as per procedure and results observed were asfollowing.

The physical characteristic like Organoleptic properties of drug was performed the results were found to be color-white powder, taste-bitter, odour-odourless and drug sample was found to be as per specifications.

Table 6.3 Organoleptic properties of Tolmatine sodium.

Test	Standard	Observation
Colour	White crystalline	White
Odour	Odour less	Odour less
Taste	Bitter	Bitter

The solubility of the drug was found to be as per specification. Result indicated that the drug is sparingly soluble in water, soluble in phosphate buffer pH 5.8 and in 0.1 N HCl.

Table 6.4 Solubility profile of drug.

S. No.	solvent	Solubility
1	Water	Sparingly soluble
2	Phosphate buffer 5.8	Soluble
3	methanol	Soluble
4	0.2 N HCl	Soluble

S. No.	Parameter	Observation
1	Bulk density (g/cm^3)	0.702 ± 0.03
2	Tapped density (g/cm^3)	0.847 ± 0.04
3	Angle of repose (θ)	32.07º± 0.20
4	Carr's index (%)	18 ± 0.40
5	Hausner's ratio	1.20 ± 0.05

The melting point was determined by melting point apparatus. It was found to in the range 207^0C as per specification. The melting point showed that the drug sample was authenticated.

Table 6.5: Melting point of drug.

Drug	Specified	Observations
Tolmatine sodium	210^0C	207^0C

Compatibility study of Tolmatine sodium

Compatibility study of drug is done by infrared spectroscopy and physical observation and it was concluded from the IR study that there was no chemical degradation of drug when it was mixed with the excipients as the characteristics absorption peaks did not changed when it was mixed with the excipients and matched with the absorption peaks of standard drug spectra.

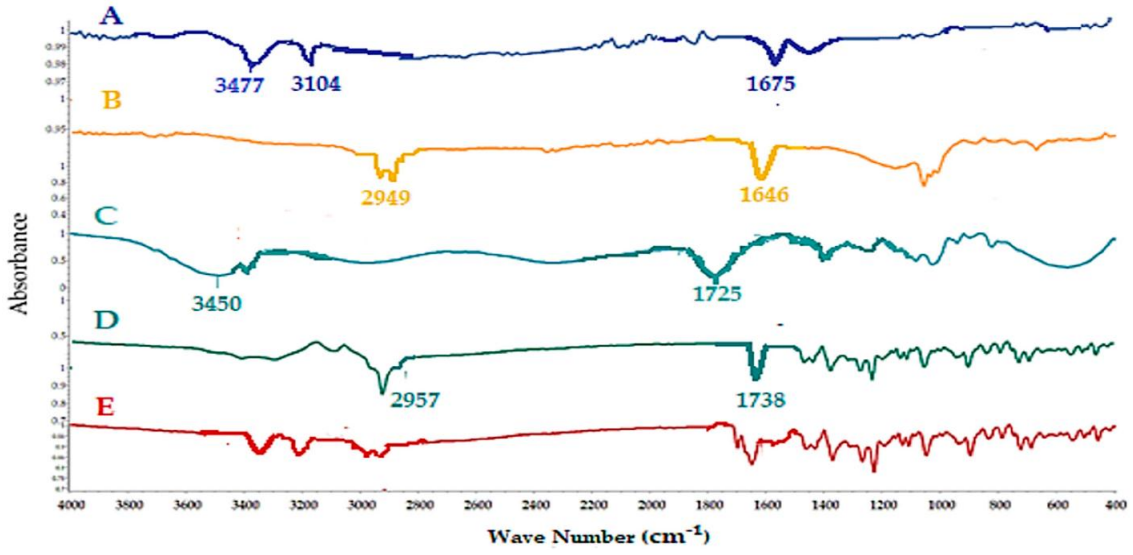


Figure No. 6.2: IR spectra of mixture of drug and excipient.

Table 6.6 Infra red characteristics of Tolmatine sodium drug sample.

S. No.	Wave no.(cm-1)	Interpretations
1.	1588.60	Ketone carbonyl (C=O) Group
2.	1675.48	Carbonyl group of carboxylic acid
3.	1750	Methylene Group
4.	3104.03	C-H Stretching Vibration

Identification by UV

Identification and authentication of drug sample was also done by ultraviolet spectroscopy and it was scanned in the range of 200-400 mm. Drug absorption maximum was found to be at 322 nm as per specification and this result indicates the purity of thedrug.

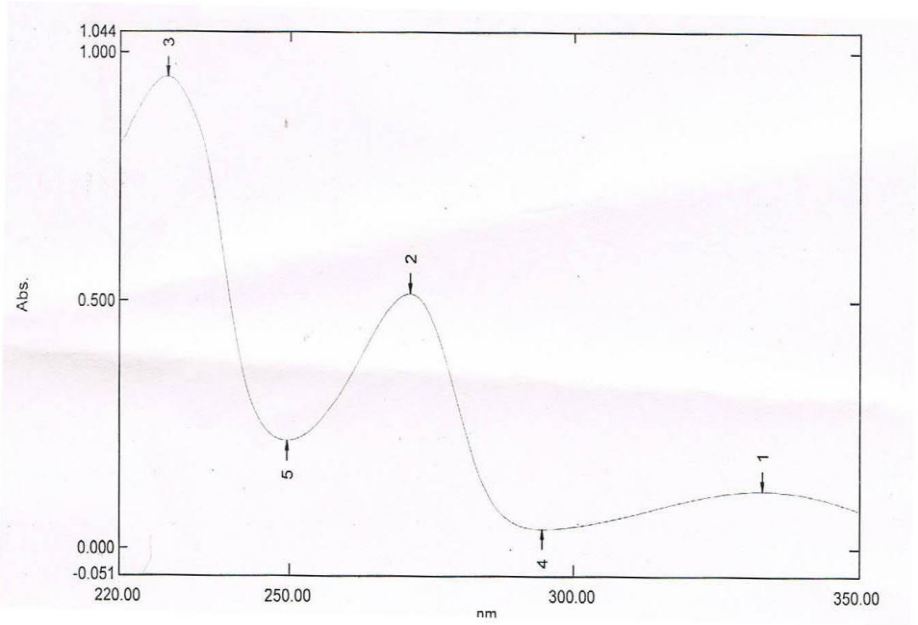


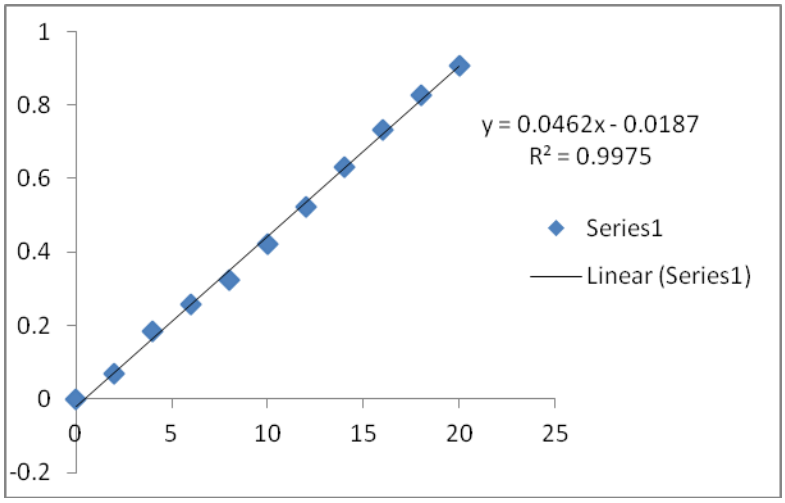
Figure No. 6.3 UV spectra of the sample drug.

The calibration curve for drug in 0.1N HCl was in the concentration range of 2-20 µg/ml and the R^2 value was calculated as 0.9975. This indicated linearity of the graph.

Table-6.7 Standard calibration curve of Tolmatine sodium in 0.1N HCl (λ max = 322 nm).

S. No.	Concentration in (µg/ml)	Absorbance
1	0	0
2	2	0.111
3	4	0.165
4	5	0.210
5	8	0.279
5	10	0.349
7	12	0.419

8	14	0.480
9	15	0.539
10	18	0.590
11	20	0.549



For Immediate Release Layer

Table: 6.8 Hardness test for immediate release layer.

Parameter	Formulation Code		
Hardness (kg/cm2)	I 1	I 2	I 3
	4.94±0.0312	5.01±0.022	4.89±0.152

Where all values are mean ±S.D. for n=3

Table: 6.9 Percent drug content of immediate release layer.

Batch Code	% Drug Content
I 1	97.12 ±0.69
I 2	97.86 ±1.21
I 3	99.26 ±1.42

Where all values are mean ±S.D. for n=3

Table: 6.10 Friability for Immediate release layer.

Parameter	Formulation Code			Reference
%Friability	I 1	I 2	I 3	Not more than 1%
	0.74 ±0.031	0 .79 ±0.022	0.83 ±0.059	

Table: 6.11 Weight variation of immediate release layer.

Parameter Weight Variation	Observation (mg)	Reference (Lachman et al.,1991)
I 1	120.0 ±0.270	±10%
I 2	120.1 ±0.170	±10%
I 3	120.2 ±0.070	±10%

Where all values are mean ± S.D. for n=3

Table: 6.12 Disintegration test of immediate release layer.

Batch Code	Disintegration time (sec.)
I 1	42 ±2.51
I 2	35 ±3.19
I 3	28 ±2.10

Where all values are mean ±S.D. for n=3

Table: 6.13 In-Vitro dissolution studies of immediate release layer.

S. No.	Time (min.)	% Drug release I 1	% Drug release I 2	% Drug release I 3
1	0	0	0	0
2	5	15	25	32
3	10	42	62	73
4	15	66	78	84
5	20	79	87	94
6	25	85	92	96
7	30	92	96	98

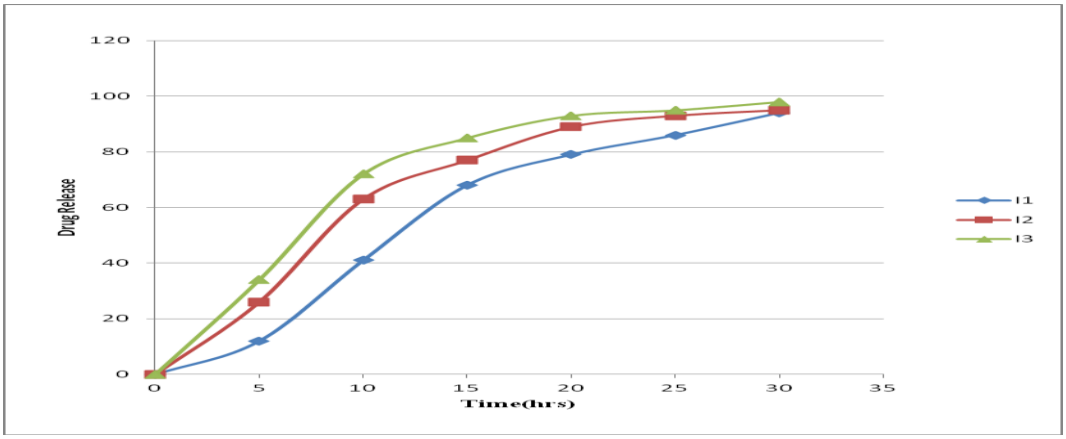


Figure: 6.5 Cumulative % drug release of immediate release of Tolmatine sodium I1, I2, I3.

On the basis of above parameters, in case of Tolmatine sodium tablet immediate layers, the formulation I 3 were found to be best on the basis of following crucial factors like hardness and drug content result was found to be 4.89±0.152 kg/cm^2 and 99.26 ±1.42. On the basis of disintegration and dissolution studies, I 3 was found to be superior amongst them which show disintegration time 28 ±2.10 second and 98% drug release.

For Sustained Release Layer

Table: 6.12 Hardness test for sustained release layer.

Batch Code	Hardness(Kg/cm2)
S1	5.0± 0.41
S2	4.9 ± 0.41
S3	5.4 ± 0.31
S4	4.7 ± 0.39
S5	4.9 ± 0.51
S6	5.5 ± 0.52
S7	5.4 ± 0.29
S8	5.5 ± 0.21
S9	5.5± 0.15

Where all values are mean ±S.D. for n=3

Table 6.13 Friability for sustained release layer.

Batch Code	%Friability	Reference
S1	0.64 ±0.053	Not more than 1%
S2	0.65 ±0.041	Not more than 1%
S3	0.70 ±0.033	Not more than 1%
S4	0.74 ±0.039	Not more than 1%
S5	0.75 ±0.051	Not more than 1%
S6	0.79 ±0.052	Not more than 1%
S7	0.81 ±0.029	Not more than 1%
S8	0.82 ±0.055	Not more than 1%
S9	0.87 ±0.059	Not more than 1%

Where all values are mean ±S.D. for n=3

Table: 6.14 Percent drug content of sustained release layer.

Batch Code	% Drug Content
S 1	93.32 ±0.54
S 2	95.26 ±0.62
S 3	97.86 ±0.90
S 4	95.25 ±1.23
S 5	96.76 ±1.76
S 6	97.55 ±1.59
S 7	97.23 ±1.79
S 8	97.43 ±1.85
S 9	98.23 ±1.53

Where all values are mean ±S.D. for n=3

Table: 6.15 Weight variation of sustained release layer.

Parameter Weight Variation	Observation (mg)	Reference (Lachman et al.,1991)
S 1	297.2 ±2.070	±7.5%
S 2	298.2 ±1.070	±7.5%
S 3	298.6 ±0.670	±7.5%
S 4	298.5 ±0.770	±7.5%
S 5	297.5 ±1.730	±7.5%
S 6	297.7 ±1.600	±7.5%
S 7	298.5 ±0.700	±7.5%
S 8	298.6 ±0.600	±7.5%
S 9	298.8 ±0.500	±7.5%

Table: 6.16 *In-Vitro* dissolution studies of sustained release layer.

S. No.	Time (in hrs.)	% Drug Release								
		S1	S2	S3	S4	S5	S6	S7	S8	S9
1	0	0	0	0	0	0	0	0	0	0
2	1	15	14	12	11	10	9	9	8	8
3	2	30	28	27	25	24	23	21	21	18
4	6	55	52	49	46	43	39	36	33	30
5	10	75	73	70	67	63	60	57	53	50
6	15	80	78	75	73	70	65	62	60	57
7	18	95	95	93	90	85	82	78	75	73
8	24	97	98	97	98	98	97	98	97	95

6 Cumulative % drug release of sustained release layer of Tolmatine sodium S1 to S9

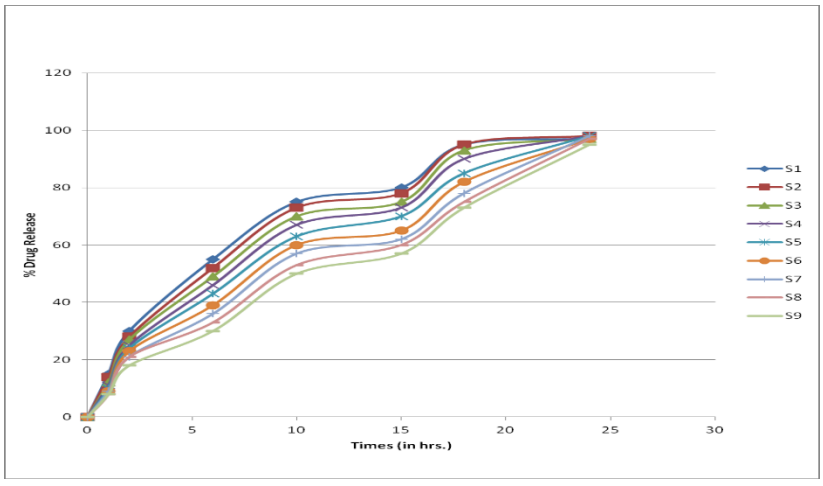


Figure: 6.

Table: 6.17 Hardness test of bilayer tablet.

Parameter	Observation (Kg/cm^2)
Hardness	7.3±0.19

Table 6.18 Ingredients Used In Formulation of Compressed Bilayer Tablet.

S. No.	Formula (In mg)	Formula for Bilayer tablet	
		I 3	S 9
1	Tolmatine sodium	70	130
2	Crosspovidone	10	-
3	Mannitol	86	15
4	Magnesium stearate	1.42	1.42
5	HPMC (K4M)	-	150
6	HPMC (K100M)	-	100
7	Talc	2.85	2.85

Where all values are mean ± S.D. for n=3

Table: 6.19 Friability of bilayer tablet.

Parameter	Observation (%)	Reference
% Friability	0.74±0.059	Not more than 1%

Where all values are mean ± S.D. for n=3

Table: 6.20 Weight variation of bilayer tablet.

Parameter	Observation(mg)	Reference (Lachman et al.,1991)
Weight Variation	415.8±4.077	±5%

Where all values are mean ± S.D. for n=3

Table: 6.21 Disintegration time for bilayer tablet.

Parameter	Observation
Disintegration time (sec.)	28.16±1.47

Where all values are mean ± S.D. for n=3

Table: 6.22 Percent Drug content in bilayer tablet.

Drug	Observation (%)
Tolmatine sodium	96.22± 2.16%

Where all values are mean ± S.D. for n=3

Table: 6.23 Cumulative percentage drug release of bilayer tablet.

Sr. No.	Time (hr.)	% Cumulative drug release
1	0	0
2	1	26.40
3	2	33.31
4	3	41.17
5	4	44.79
6	5	48.70
7	6	52.24

8	7	56.80
9	8	61.59
10	9	64.89
11	10	70.16
12	11	75.29
13	12	80.89
14	14	83.16
15	16	89.31
16	24	96.63

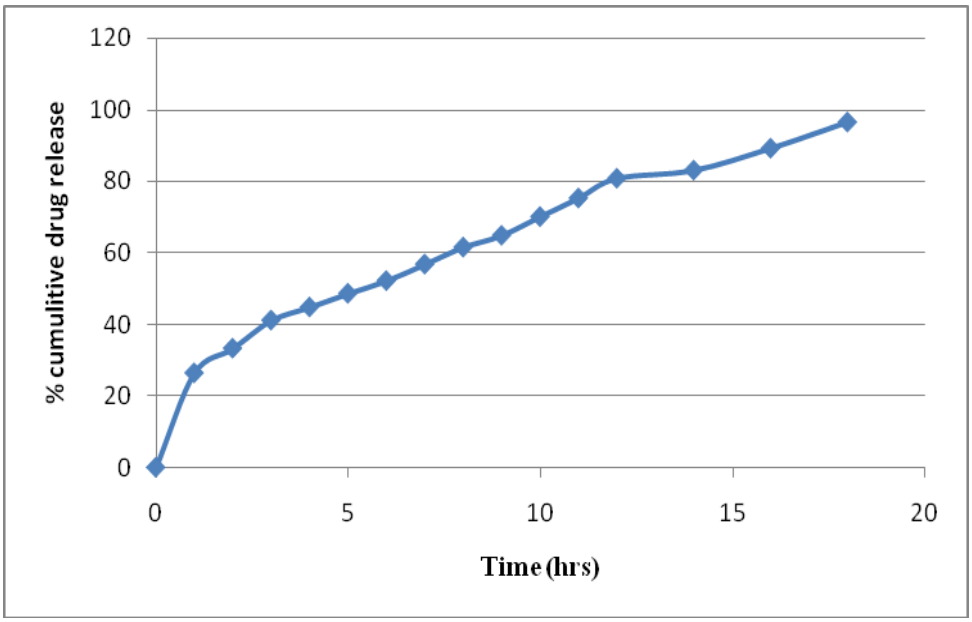


Figure: 6.7 Cumulative percent drug release of Tolmatine sodium bilayer tablet.

7. SUMMARY AND CONCLUSION

7.1 Summary

Preformulation study is an important parameter for any pharmaceutical formulation design, it can be said that it is the first step in the development of dosage form. It can be defined as an investigation of physical and chemical property of a substance alone and when combined with excipients. Various preformulation study parameters were investigated and the results of it are described below.

The identification and authentication of drug sample was performed on the basis of IR spectroscopy, UV spectroscopy and melting point determination. IR spectroscopy was performed by KBr pellets technique and the spectrum was recorded on Shimadzu 8400-S FTIR spectrophotometer, Japan. Spectrum of IR spectroscopy matched with standard spectrum band.

Ultraviolet spectroscopy was performed using UV visible spectrophotometer (Shimadzu 1700, Japan). The sample was scanned in the range of 200-400 nm and spectra showed the λ_{max} at 322 nm. From the result λ_{max} obtained from sample spectrum is matched with the standard drug absorption as per the standard monograph thus, it shows the drug was Tolmatine sodium.

The melting point of drug was determined to check the purity of the drug. Melting point was observed in the range of 207 °C for Tolmatine sodium which comply with the standard.

Organoleptic properties tests were performed as per procedure given in experimental part. Colour, odour, and taste were found as white, odourless and bitter for Tolmatine sodium respectively which was found as per the specified monograph. From these parameters it was concluded that the available drugs were Tolmatine sodium.

Micromeritic property was performed to study flow of the powders from the above study the angle of repose, bulk density and true density of the bulk powder was fond to be 32.07º±0.20, 0.702 ±0.03 g/cm^3 and 0.847 ±0.04 g/cm^3 respectively. The compressibility index was found to be 18 ±0.40% and Hausner's ratio was found 1.20 ±0.05. This result was showing good compression properties and good flow properties.

The solubilization study was carried out by making calibration curve in 0.1N HCl was found R^2 = 0.9975 which was near to one and showed linearity of the graph.

The present study was carried out to perform the identification and preformulation.