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Formulation and Evaluation of Tolmetin Sodium COX-2 Inhibitors for Treatment of Osteoarthritis

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Abstract

The aim of the present research work is to "Formulation and Evaluation of Tolmetin Sodium COX-2 Inhibitors for treatment of Osteoarthritis 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 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 small intestine. [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 oraldrug delivery system consists of basic understanding of the following three aspects:

- Physicochemical, pharmacokinetic &pharmacodynamics of thedrug.
- The Anatomical and physiological characteristics ofGIT.
- Physicochemical characteristics & drug delivery system and type of dosage form

design. [3]

Controlled Drug Delivery System

A controlled release formulation may increase the efficacy of compound and it may improve the patient compliance as reduced in dosing frequency. CR form is that releases one or more drug at fixed rate and time either in blood or at targeted organ. [31]

MATERIAL & METHODS

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.

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

Solubility Analysis

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

MELTING POINT:

Melting point of drug:

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

ANGLE OF REPOSE

Table: Angle of Repose Guidelines

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

Formulation of Tolmatine sodium Immediate Release Layer

Composition of Tolmatine sodium Immediate Release Layer

Ingredient (mg)	I1	I2	I3
Tolmatine sodium	70	70	70
Crosspovidone	2	5	10
Mannitol	94	91	86
Magnesium stearate	1.42	1.42	1.42
Talc	2.85	2.85	2.85

Formulation of Tolmatine sodium Sustained ReleaseLayer

Composition of Tolmatine sodium Sustained release layer

Ingredient (mg)	S1	S2	S3	S4	S5	S6	S7	S8	S9
Tolmatine sodium	130	130	130	130	130	130	130	130	130
HPMC (K4M)	100	100	100	125	125	125	150	150	150
HPMC K100M	60	80	100	60	80	100	60	80	100
Mannitol	95	75	55	75	55	35	55	35	15
Magnesium stearate	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42
Talc (mg)	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85

All the batches contained 2% w/w talc and 1% w/w magnesium stearate.

RESULTS AND DISCUSSION

Table: 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: 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: Organoleptic properties of Tolmatine sodium

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

Table: 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

Table: Melting point of drug

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

For Immediate Release Layer:

Table: 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=

Table: 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: 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: 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: 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: 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

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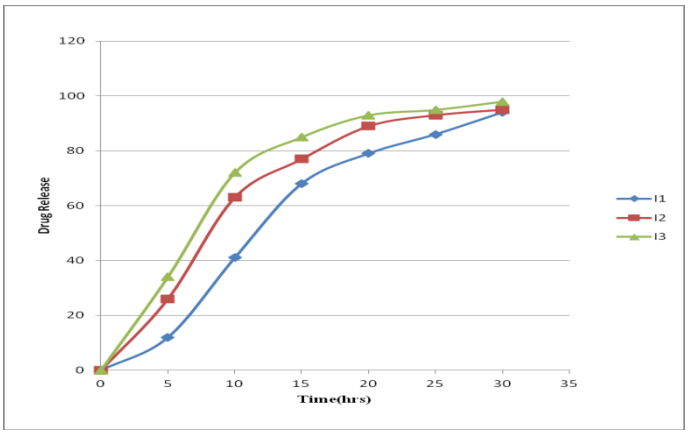

Figure: Cumulative % drug release of immediate release of Tolmatine sodium I1, I2, I3

Sustained Release Layer:

Table: 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: 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: 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: 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%

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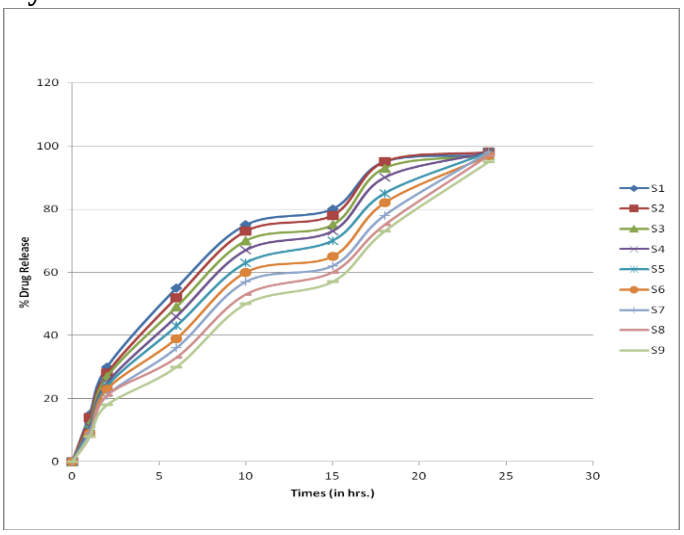
S 9	298.8 ±0.500	±7.5%

Table: 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 S



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

Table: 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: 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: 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: 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: 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

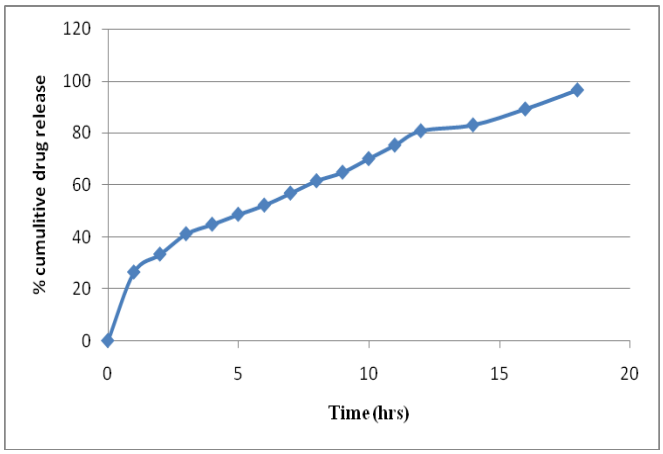


Figure: Cumulative percent drug release of Tolmatine sodium bilayer tablet

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