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(RESEARCH ARTICLE)

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Optimization and evaluation of bilayer tablet of probenecid

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Abstract

The main objective of my research work is to develop a bilayer tablet of Probenecid, 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. Probenecid is frequently administered up to 3 times in a day. So, the reducing dosing frequency by sustained release tablet.

Keywords: Sustained; Immediate; Probenecid; Optimizing; Frequency.

1. 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.

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.

Drugs that are easily absorbed from the GIT and have a short half-life are eliminated quickly from the blood circulation so they require frequent dosing. To avoid this drawback, the oral sustain/controlled release formulation have been developed in an attempt to release the drug slowly in to the GIT and maintain the effective drug concentration in the serum for longer period of time.

All the pharmaceutical formulation for systemic effect via oral route of 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 three aspects:

- Physicochemical, pharmacokinetic & pharmacodynamic characteristics of the drug.
- The Anatomical and physiological characteristics of GIT.
- Physicochemical characteristics & drug delivery system and type of dosage form design.

The manufacture of multilayer tablets has been successful for over 50 years and one of the early scientific evaluations of layered tablets was published by Stephenson (1961). New machine designs developed during the late 60s have made it possible to check the weight of individual layers by sampling without stopping the machine, providing in-process control facilities to ensure correct dosing, however, despite this, a considerable amount of expertise is still required to formulate these tablets and to ensure consistent manufacture to satisfy regulatory requirements. One problem that

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causes great concern is the delamination of layered tablets which has become a more obvious problem with the increase in compression speed on modern high-speed rotary machines.

2. Materials and methodology

Table 1 List of Materials

S. No.	Ingredients	Category
1	Probenecid	Drug
2	Cross povidone	Super disintegrants
3	Hydroxypropyl methyl cellulose	Rate controlling polymer
4	Microcrystalline cellulose	Filler
5	Magnesium stearate	Glident
6	Talc	Lubricant

Table 2 List of Equipment

S. No	Instrument Used	Manufacturer
1	Electronic weighing balance	Mettler, Switzerland
2	Max mixer	Innofab India pvt.ltd,Hyderabad
3	Fluidized bed dryer	Alliance, Bombay
4	Cadmill	Cadmach, Ahemedabad
5	Tablet Compression Machine 45 stationdouble rotary	Cadmach, Ahemedabad
6	Friability Tester	Veego, Mumbai
7	Tablet Hardness Tester	Electrolab, Mumbai
8	Bulk density apparatus	Electrolab, Mumbai
9	Blender	Bhuvaneswari, Mumbai
10	Dissolution Apparatus	Veego, Mumbai
11	Tablet Disintegeration Apparatus	Veego, Mumbai
12	FT-IR Spectrophotometer	Perkin Elmer, USA

3. Results and discussion

3.1. Pre-formulation Studies

Table 3 Physical properties of Probenecid

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

Table 4 Solubility profile of drug

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

Table 5 Melting point of drug

Material	Specified	Observations
Probenecid	1940C-1960C	1930C-1950C

Table 6 Loss on drying

S. No.	Specification	Observation
1	NMT 0.5%	0.350%±0.02

Table 7 Partition Coefficient of drug sample

Material	Observation
Probenecid	1.57±0.13

Table 8 The flow parameters of drug powder observed

S. No.	Parameter	Observation
1	Bulk density (g/cm3)	0.704 ± 0.04
2	Tapped density (g/cm3)	0.847 ± 0.05
3	Angle of repose (θ)	32º.07”± 0.20
4	Carr’s index (%)	18 ± 0.40
5	Hausner’s ratio	1.20 ± 0.05

3.2. Identification and Authentication of Drug

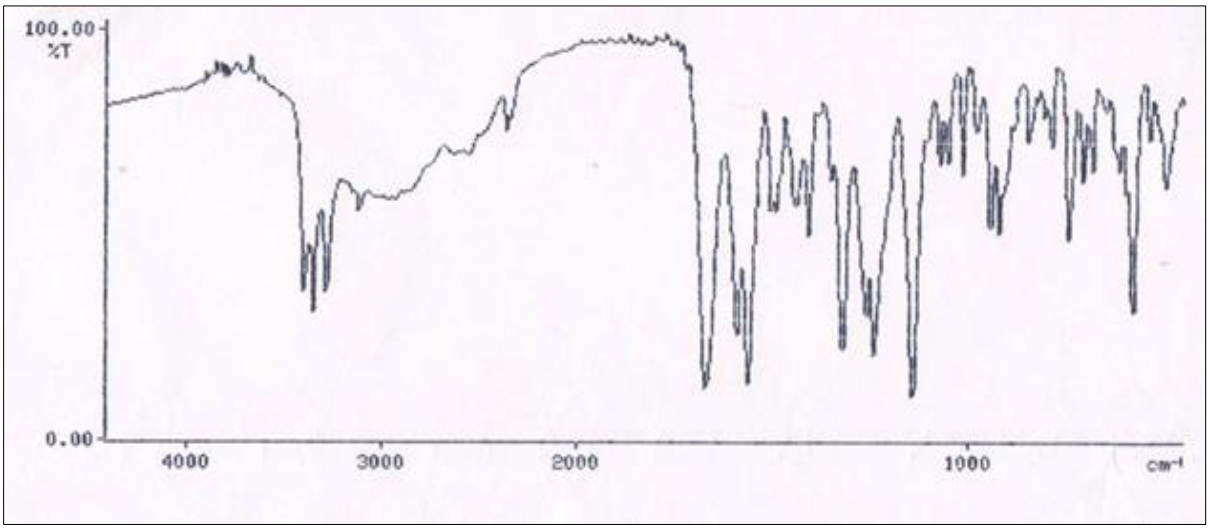

Figure 1 IR spectra of Drug

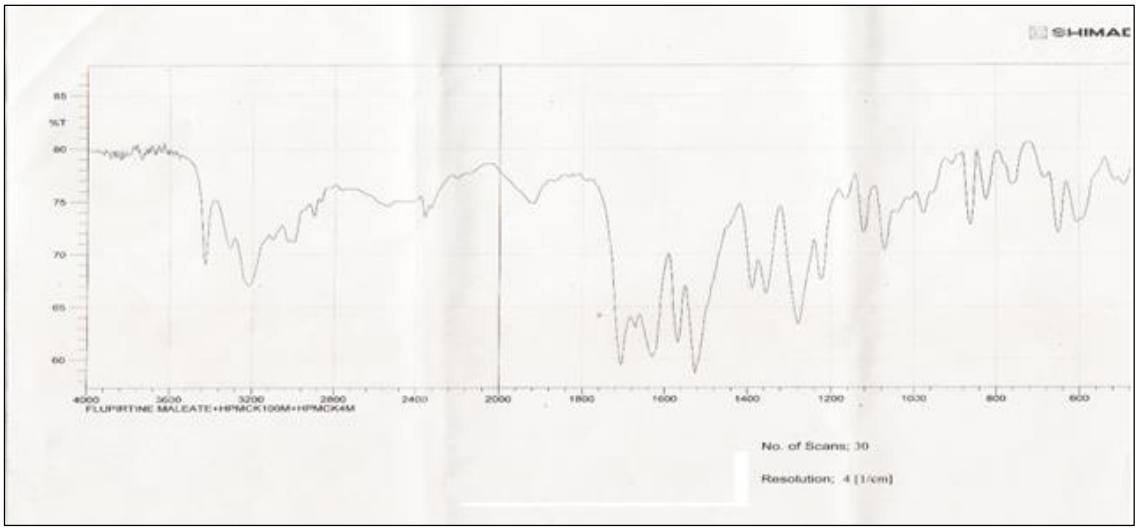

Figure 2 IR spectra of mixture of drug and excipient

Table 9 Infrared characteristics of Probenecid drug sample

S. No.	Wave no.(cm-1)	Interpretations
1.	700-800	Alkanes (C-C Stretching)
2.	1015	C-H Bending Vibrations
3.	1120	Alcoholic C-O Stretching
4.	1150	Methylene Group
5.	1720	C=O Stretching
5.	3200-3400	C-H Stretching of Alkynes

3.3. Ultraviolet spectroscopy

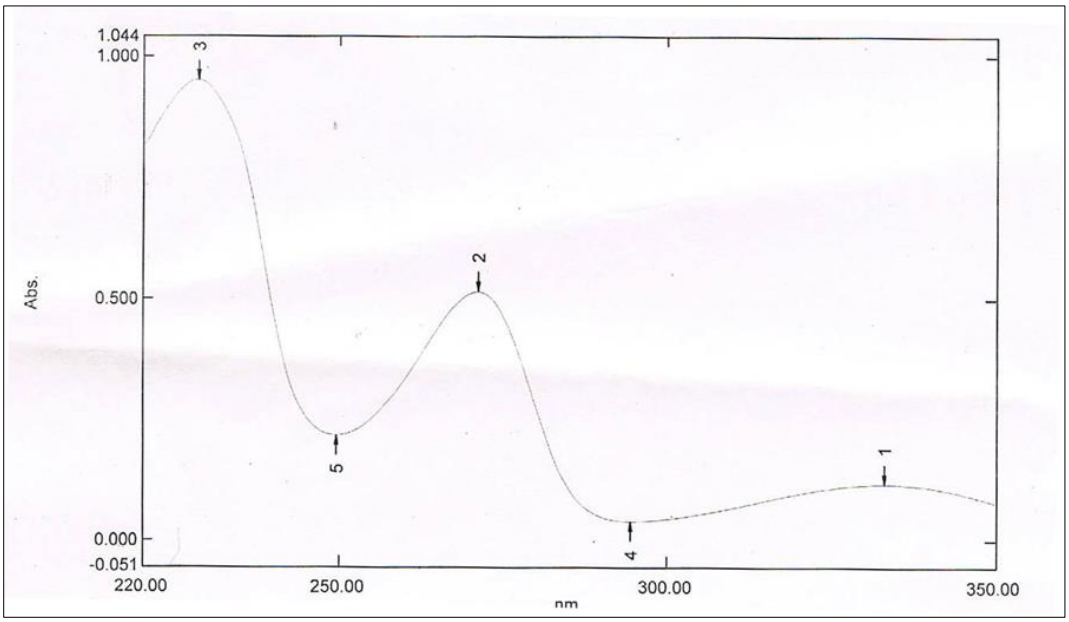

Figure 3 UV spectra of the sample drug

3.4. Optimization methodologies

Table 10 Composition of Probenecid tablet layers (Immediate)

Ingredients(Quantity in mg)	I1	I2	I3
Probenecid	250	250	250
Cross povidone	2(1%)	5(2.5%)	10(5%)
Mannitol	94	91	86
Magnesium stearate	2	2	2
Talc	2	2	2
Total Weight	350 mg		

Table 11 Composition of Probenecid tablet layer (Sustained)

Composition (mg)	Formulation code								
	S1	S2	S3	S4	S5	S6	S7	S8	S9
Probenecid	250	250	250	250	250	250	250	250	250
HPMC K4M	40	40	40	60	60	60	80	80	80
HPMC K100M	60	80	100	60	80	100	60	80	100
Mannitol	95	75	55	75	55	35	55	35	15
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	450 mg								

3.5. Optimization Parameters

Table 12 Hardness test for immediate release layer

Parameter	Formulation Code		
Hardness (kg/cm2)	I 1	I 2	I3
	2.5±0.22	3.02±0.25	2.9±0.16

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

Table: 13 Hardness test for sustained release layer

Batch Code	Hardness (Kg/cm2)
S1	5.2 ± 0.41
S2	4.9 ± 0.42
S3	5.4 ± 0.35
S4	4.5 ± 0.46
S5	4.7 ± 0.52
S6	5.8 ± 0.56
S7	5.4 ± 0.38
S8	5.5 ± 0.25
S9	5.5± 0.15

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

Table 14 Percent drug content of immediate release layer

Batch Code	% Drug Content
I1	97.12 ±0.75
I2	97.86 ±1.22
I3	99.26 ±1.45

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

Table 15 Percent drug content of sustained release layer

Batch Code	% Drug Content
S1	99.32 ± 2.28
S2	97.68 ±2.54
S3	98.22 ±3.34
S4	99.63 ±2.12
S5	98.54 ±4.23
S6	97.80 ±3.22
S7	99.41 ±1.86
S8	96.80 ±2.33
S9	98.25 ±3.67

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

Table 16 *In-vitro* dissolution studies of immediate release layers of Probenecid

S.No.	Time(min.)	I 1	I 2	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

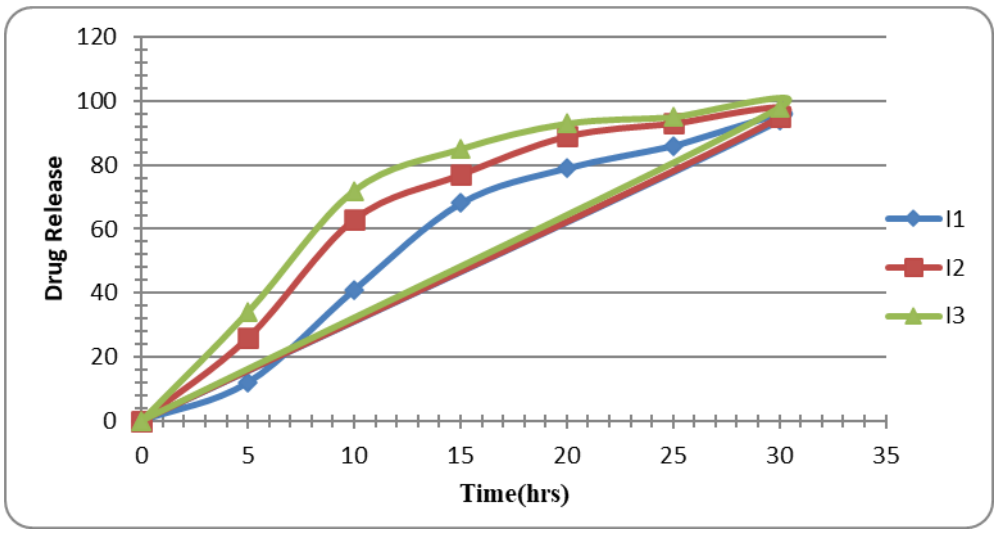

Figure 4 Cumulative % drug release of immediate release tablet I1, I2, I3

Table 17 *In-vitro* dissolution studies of sustained release layers of Probenecid

S.No.	Time (hrs)	S1	S2	S3	S4	S5	S6	S7	S8	S9
1	0	0	0	0	0	0	0	0	0	0
2	1	5.82	5.46	5.53	4.87	6.12	5.11	4.71	5.98	5.23
3	2	10.56	9.68	8.65	8.96	9.81	9.55	11.23	9.14	10.27
4	3	20.35	18.43	18.48	18.19	19.46	19.85	23.47	20.16	19.65
5	4	29.45	27.68	26.32	25.86	24.91	25.83	28.96	25.85	24.89
6	5	38.48	36.43	34.82	34.23	33.38	32.36	33.65	30.58	30.77
7	6	45.25	44.26	41.57	40.48	36.65	38.08	39.54	35.29	34.82
8	7	50.63	49.12	46.95	45.96	42.98	41.96	45.32	41.34	38.37
9	8	56.32	54.27	50.52	50.32	48.23	48.80	48.24	48.21	42.35
10	9	62.56	60.54	56.98	56.87	51.92	56.39	58.99	54.85	47.98
11	10	68.38	65.38	64.13	61.95	59.87	62.36	68.41	59.37	55.42
12	11	74.86	72.48	70.28	68.66	66.73	68.23	72.59	67.24	63.57

13	12	82.16	80.25	74.98	74.98	75.38	75.54	79.68	77.89	68.58
14	14	91.23	90.49	84.78	84.12	86.84	86.78	87.93	86.65	79.68
15	16	96.96	96.79	95.77	95.43	95.46	95.10	96.34	94.75	88.34
16	18	_	_	_	_	_	_	_		97.46

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

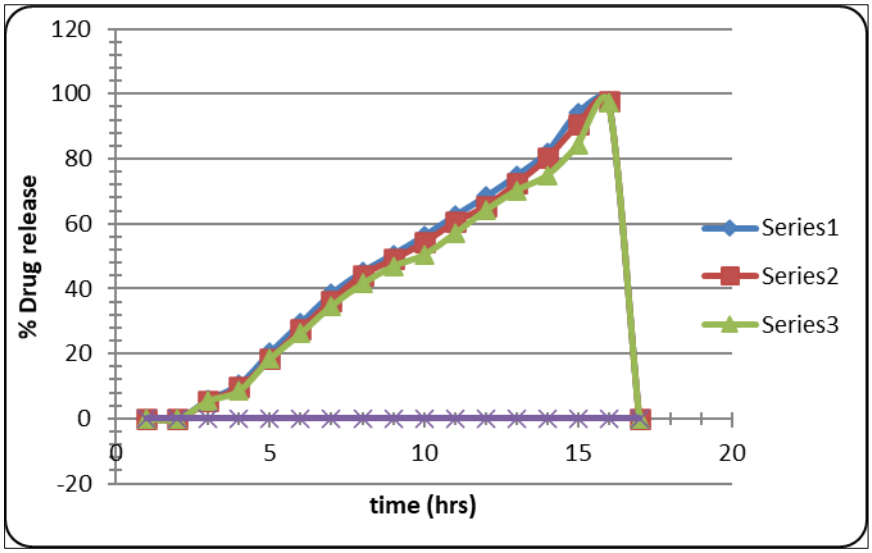

Figure 5 Cumulative % drug release of sustained release tablet S1, S2, S3 batch

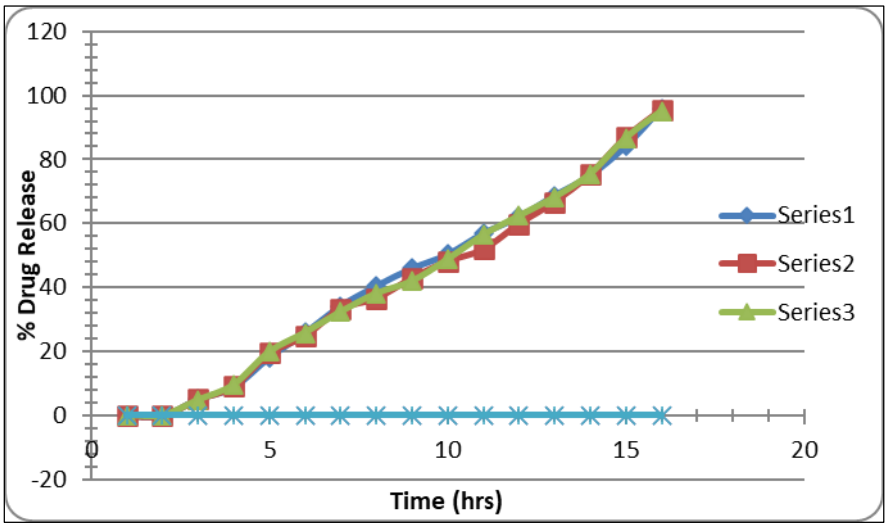

Figure 6 Cumulative percent drug release of sustained release tablet S4, S5, S6 batch

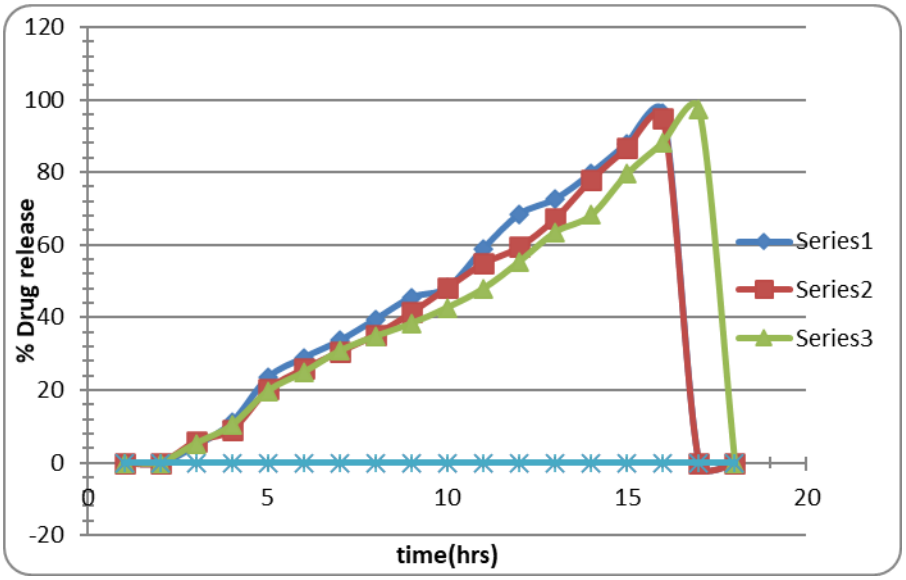

Figure 7 Cumulative percent drug release of sustained release tablet S7, S8, S9 batch

3.6. Evaluation of optimized batch

Table 18 Bulk density & tapped density of powder blend

Parameter	Immediate Layer	Sustained Lyer
Bulk density (gm/ml)	0.761	0.673
Tapped density (gm/ml)	0.894	0.831

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

Table 19 Carr's index of Probenecid layer power blend

Parameter	Powder blend of immediate release layer	Powder blend of sustined release layer
% carrs index	14.8	19.01

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

Table 20 Hausner's ratio of powder blend of different layer

Parameter	Powder blend of immediate release layer	Powder blend of sustained release layer
Hausner's ratio	1.175	1.234

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

3.7. Post compression parameters

Table 21 General appearance of bilayer tablet

Parameter	Observation
Diameter	10.0 ± 0.92mm
Thickness	7.5 ± 0.241mm
Shape	Round
Color	One layer is slightly yellow and second is white

Table 22 Hardness test of bilayer tablet

Parameter	Observation
Hardness	7.4±0.25

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

Table 23 Friability of bilayer tablet

Parameter	Observation	Rference (Lachman et al.,1991)
% Friability	0.74±0.063	Not more than 1%

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

Table 24 Weight variation of bilayer tablet

Parameter	Observation	Rference (Lachman et al.,1991)
Weight Variation	720.8±4.078	±5%

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

Table 25 Disintegration test of immediate layer of bilayer tablet

Parameter	Observation
Disintegration time (sec.)	28.16±1.48

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

Table 26 Percent Drug content in bilayer tablet

Drug	Observation
Probenecid	98.23± 2.18%

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

Table 27 Cumulative percentage drug release of bilayer tablet

Sr.No.	Time (hr.)	% Cumulative drug release
1	0	0
2	1	26.44
3	2	33.34
4	3	41.19
5	4	44.87
6	5	48.70
7	6	52.25
8	7	56.87
9	8	61.63
10	9	64.93
11	10	70.17
12	11	75.36
13	12	80.91

14	14	83.17
15	16	89.31
16	18	96.63

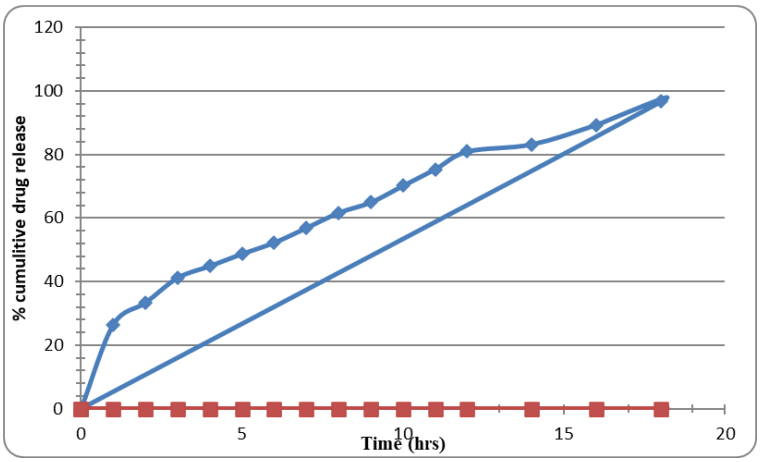

Figure 8 Cumulative percent drug release of Probenecid bilayer tablet

4. Conclusion

In the present study Probenecid 250 mg tablets have been formulated and developed using direct compression and dry granulation technique, to provide a safe, highly effective method for treating rheumatoid arthritis, pain and inflammation. While reducing undesirable adverse effects. Pre and post formulation parameters were studied for the formulated batches. The result of all the physical and in-vitro dissolution data concluded that bilayer tablet (S3, I3) was the most promising formulation. The trial conducted with the consecutive three batches revealed relative standard deviation below 2 %, indicative the insignificant batch-to-batch variation that can be overcome if processes are run out in a controlled manner.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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