ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

FORMULATION AND EVALUATION OF BUPRENORPHINE SUSTAINED RELEASE BUCCAL TABLETS

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ARTICLE INFO

Key words:
Buprenorphine, buccal tablets, sustained release, analgesic.

Access this article online
Website:
https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Buprenorphine, a novel long-acting analgesic, was developed with the intention of two purposes: analgesia and opioid use disorder. Buprenorphine was first marketed in 1985 as an opioid analgesic. It was originally a scheduled V-controlled substance in the United States and offered in a low-dose formulation. Buprenorphine is an opioid used to treat opioid addiction, acute pain, and chronic pain. It is a narcotic analgesic. It can be used under the tongue, by injection, as a skin patch, or as an implant. For opioid addiction it is typically only started when withdrawal symptoms have begun and for the first two days of treatment under direct observation of a health care provider. The aim of the present study was to develop buccal formulation of buprenorphine to maintain constant therapeutic levels of the drug for over 12 h. Various grades of HPMC were employed as polymers. Buprenorphine dose was fixed as 8 mg. Total weight of the tablet was considered as 100 mg. Polymers were used in the concentration of 4 mg, 8mg and 12 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F_8) showed better and desired drug release pattern i.e. 98.54% in 12 h. It followed Peppas release kinetics mechanism.

INTRODUCTION

Buprenorphine is a semisynthetic opioid that may offer an alternative to μ-opioid agonists. Buprenorphine exhibits partial agonism at μ-opioid receptors while maintaining a relative potency, compared with oral morphine, of between 75:1 and 115:1. In addition to partial agonism at μ-opioid receptors, buprenorphine is a κ-opioid receptor antagonist and appears to act as a "chaperone" ligand, increasing the expression of μ-opioid receptors on cell membranes[1]. It also has agonist activity at opioid receptor-like 1 (ORL1) receptors that confers both an additive analgesic effect (through activation of receptors at the dorsal horn) and an inhibitory effect (through activation of receptors in the brain)[2,3]. Activation of these receptors also leads to blockade of the rewarding effects of morphine, which suggests that ORL1 receptors may contribute to the limited tolerance observed with buprenorphine[4-7]. The aim of the present research was to develop buccal formulation of buprenorphine to maintain constant therapeutic levels of the drug for over 12 h.

MATERIALS AND METHODS

Materials: Buprenorphine, HPMC K4M, HPMC K15M, Locust bean gum, MCC pH 102, magnesium stearate, talc all the chemicals were laboratory grade[8-10].

Formulation development of tablets: All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 1. The tablets were prepared as per the procedure given below

and aim is to prolong the release of buprenorphine. Total weight of the tablet was considered as 100 mg[11-14].

Procedure: Buprenorphine and all other ingredients were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method[15-18].

Evaluation of post compression parameters for prepared tablets: The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content[19-21].

RESULTS AND DISCUSSION: The present study was aimed to developing buccal tablets of Buprenorphine using various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Analytical method: Graphs of buprenorphine as taken in buccal pH that is in p H 6.8 phosphate buffer at 255 nm. Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43 to 0.58 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations have shown the Hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Quality control parameters for tablets: Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the formulation of tablet.

***In vitro* quality control parameters for tablets:** All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In vitro* drug release studies:** From the dissolution data it was evident that the formulations prepared with Methocel K4M as polymer were unable to retard the drug release up to desired time period i.e., 12 h. Whereas the formulations prepared with Locust bean gum retarded the drug release in the concentration of 8 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.54% in 12 h with good retardation. The formulations prepared with Methocel 15M showed more retardation even after 12 h they were not shown total drug release. Hence, they were not considered.

Table 1: Formulation composition for tablets

Formulation No.	Buprenorphine	Methocel K4M	Methocel K15M	Locust bean gum	Mag. stearate	Talc	MCC pH 102
F1	8	4	-	-	3	3	QS
F2	8	8	-	-	3	3	QS
F3	8	12	-	-	3	3	QS
F4	8	-	4	-	3	3	QS
F5	8	-	8	-	3	3	QS
F6	8	-	12	-	3	3	QS
F7	8	-	-	4	3	3	QS
F8	8	-	-	8	3	3	QS
F9	8	-	-	12	3	3	QS

All the quantities were in mg.

Table 2: Observations for graph of buprenorphine in p H 6.8 phosphate buffer (255nm)

Concentration (µg/ml)	Absorbance
0	0
2	0.172
4	0.289
6	0.437
8	0.567
10	0.715
12	0.172

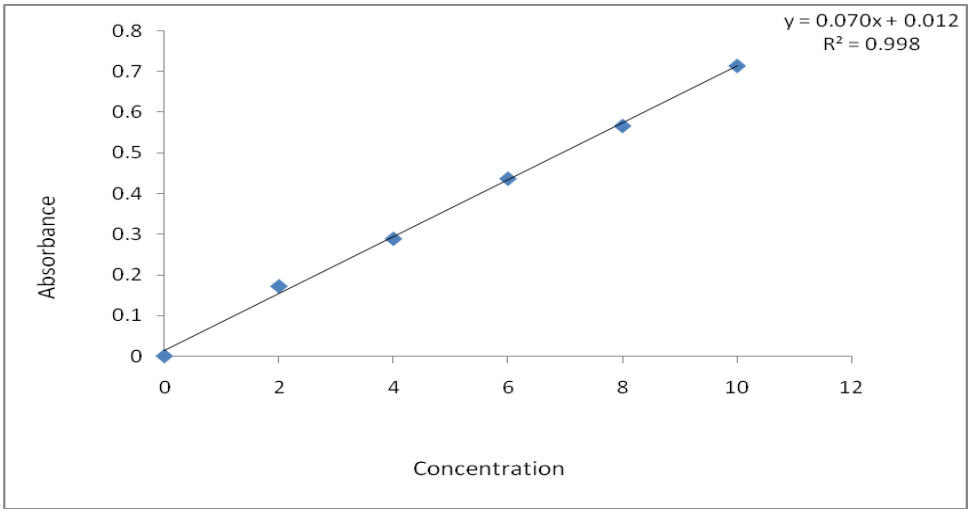

Figure 1: Standard graph of buprenorphine in pH 6.8 phosphate buffer (255nm)

Table 3: Pre formulation parameters of powder blend

Formulation code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.43	0.56	16.19	0.98
F2	25.67	0.45	0.57	16.87	0.87
F3	25.54	0.46	0.58	16.77	0.78
F4	25.43	0.47	0.63	17.82	0.99
F5	25.34	0.49	0.67	17.88	1.19
F6	24.22	0.58	0.69	16.29	1.20
F7	25.18	0.54	0.57	17.86	1.09
F8	24.22	0.51	0.58	17.88	1.19
F9	25.05	0.54	0.58	18.00	1.18

Table 4: Post compression parameters

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	98.5	4.5	0.48	2.2	98.42
F2	101.4	4.4	0.43	2.3	98.35
F3	98.6	4.3	0.42	2.3	99.62
F4	100.6	4.5	0.45	2.2	97.74
F5	99.4	4.3	0.60	2.6	98.42
F6	100.7	4.2	0.52	2.3	99.33
F7	102.3	4.5	0.54	2.5	99.52
F8	101.2	4.4	0.52	2.3	98.61
F9	98.3	4.5	0.53	2.4	99.19

Table 5: Dissolution data of buprenorphine tablets prepared with HPMC K4M in different concentrations

Time (h)	Cumulative percent drug released		
	F1	F2	F3
0	0	0	0
1	9.45	5.45	4.56
2	17.46	14.78	1.467
3	25.65	21.76	28.62
4	38.71	31.76	37.43
5	49.62	42.87	46.92
6	54.35	49.63	54.43
7	65.51	56.43	64.13
8	71.54	67.56	75.34
9	77.82	73.67	78.42
10	81.13	78.56	82.18
11	85.59	83.09	85.98
12	89.09	87.88	88.79

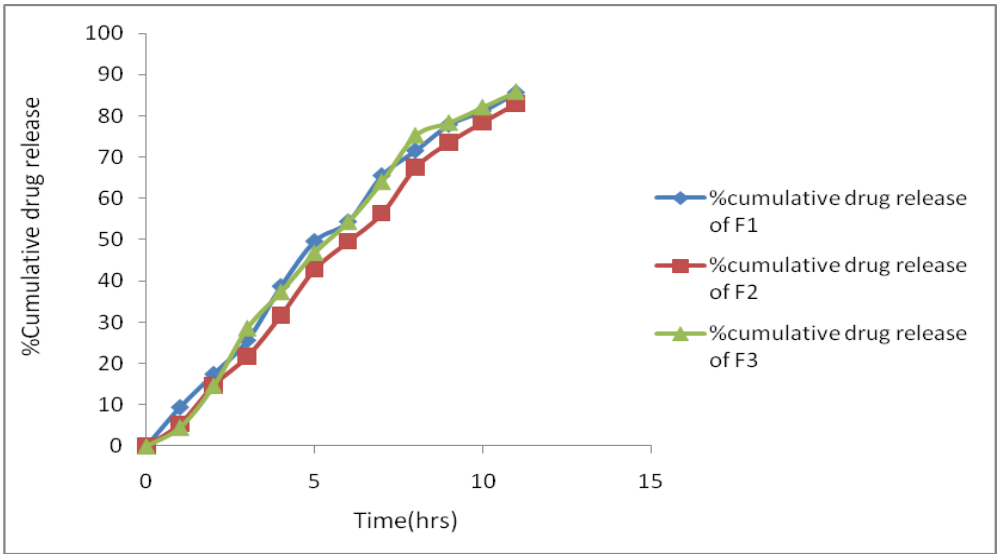

Figure 2: Dissolution profile of buprenorphine (F_1, F_2, F_3 formulations)

Table 6: Dissolution data of buprenorphine tablets prepared with HPMC K15M in different concentrations

Time (h)	Cumulative percent drug released		
	F4	F5	F6
0	0	0	0
1	7.54	9.56	6.65
2	16.56	18.75	13.78
3	21.87	24.74	22.18
4	34.1	32.54	29.89
5	42.98	38.27	37.67
6	54.92	42.75	45.91
7	63.77	49.63	52.41
8	71.65	54.75	58.98
9	74.56	59.17	67.65
10	81.19	65.32	73.71
11	84.34	72.39	76.98
12	88.98	78.98	83.29

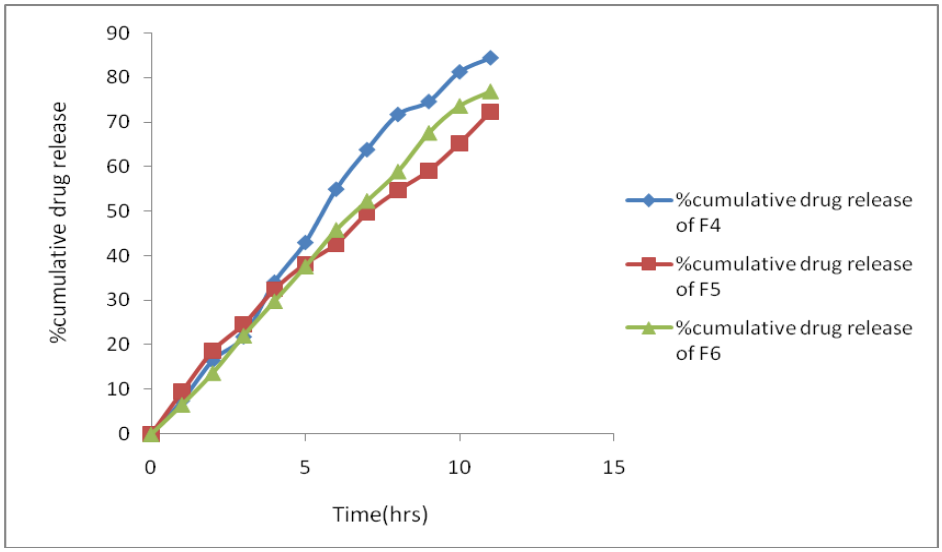

Figure 3: Dissolution profile of buprenorphine (F_4, F_5, F_6 formulations)

Table 7: Dissolution data of buprenorphine tablets prepared with Locust bean gum in different concentrations

Time (h)	Cumulative percent drug released		
	F7	F8	F9
0	0	0	0
1	7.31	8.71	6.53
2	12.67	17.65	14.53
3	19.78	25.76	21.71
4	26.76	36.71	28.56
5	34.78	43.41	35.43
6	43.76	54.81	43.31
7	52.87	64.76	51.31
8	61.61	69.61	58.67
9	68.76	76.45	66.91
10	79.94	83.16	76.31
11	83.98	91.56	82.29
12	85.67	98.54	85.49

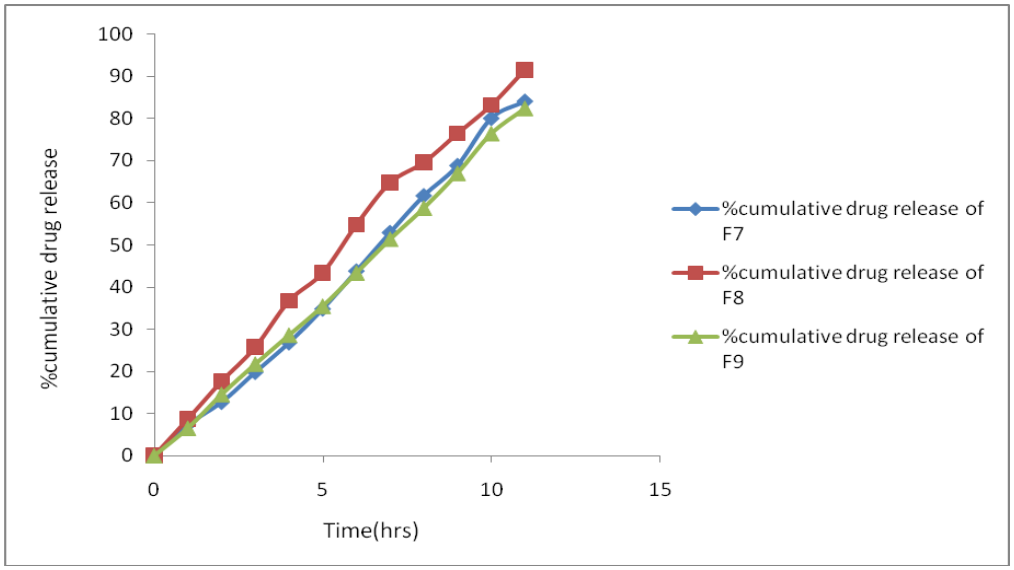

Figure 4: Dissolution profile of Buprenorphine (F_7, F_8, F_9 formulations)

Table 8: Release kinetics data for optimised formulation

Cumulative (%) release Q	Time (T)	Root (T)	Log (%) release	Log (T)	Log (%) remain
0	0	0			2.000
8.71	1	0.458	0.940	1.987	1.960
17.65	2	1.000	1.247	0.000	1.961
25.76	3	1.414	1.411	0.301	1.871
36.71	4	1.732	1.565	0.477	1.801
43.41	5	2.000	1.638	0.602	1.753
54.81	6	2.236	1.739	0.699	1.655
64.76	7	2.449	1.811	0.778	1.547
69.61	8	2.646	1.843	0.845	1.483
76.45	9	2.828	1.883	0.903	1.372
83.16	10	3.000	1.920	0.954	1.226
91.56	11	3.162	1.962	1.000	0.926
98.54	12	3.317	1.994	1.041	0.164

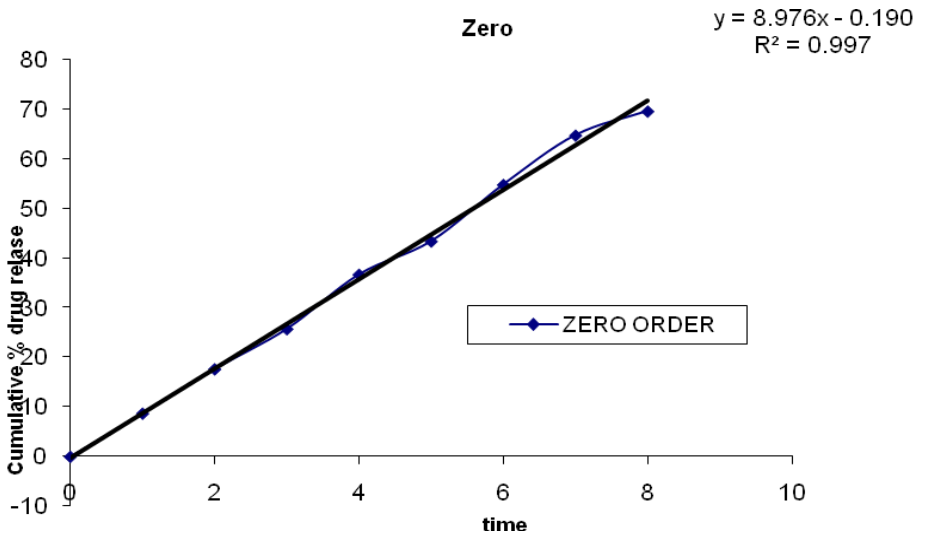

Figure 5 : Zero order release kinetics graph

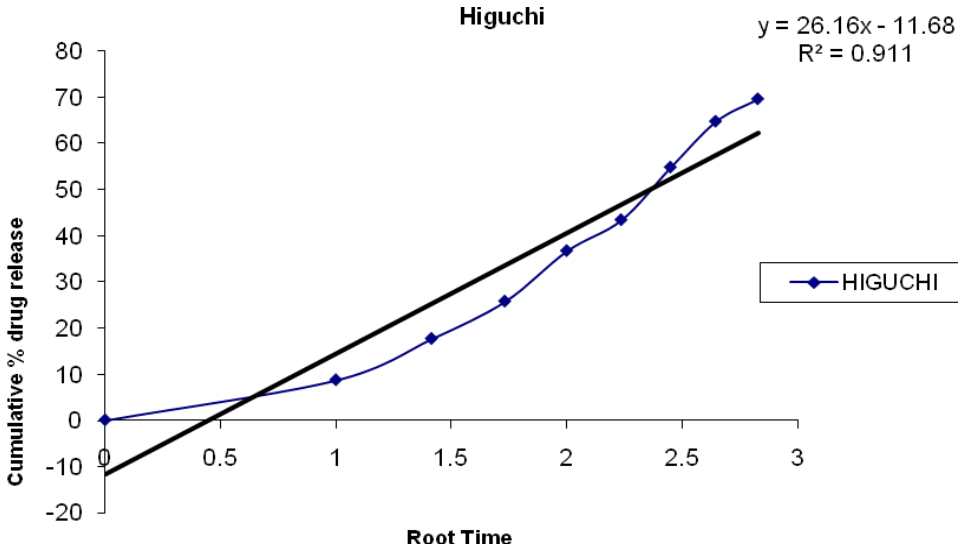

Figure 6 : Higuchi release kinetics graph

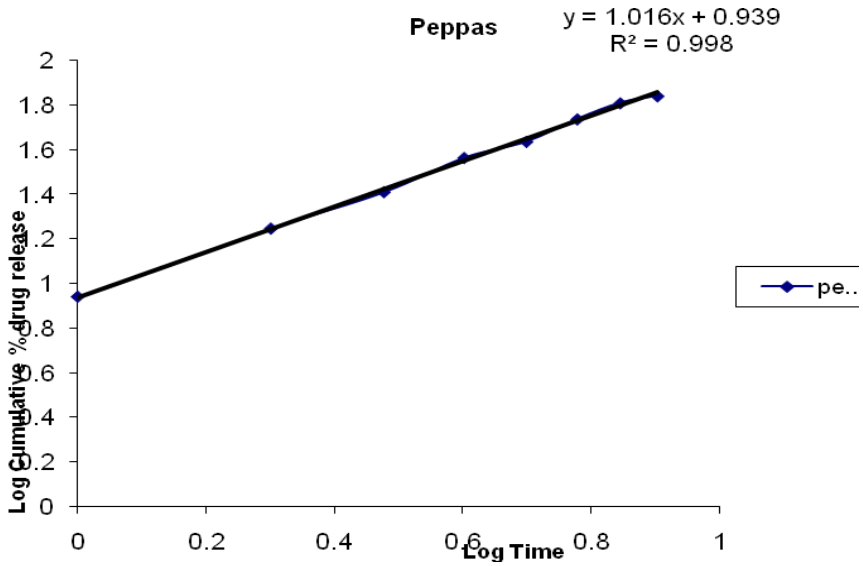

Figure 7: Kars mayer peppas graph

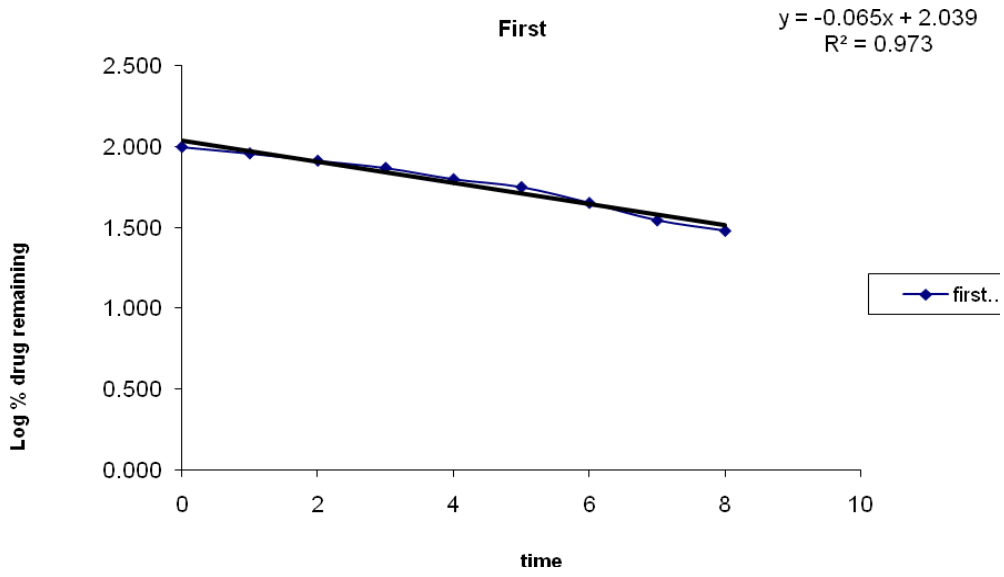

Figure 8: First order release kinetics graph

From the above graphs it was evident that, the formulation F_8 was followed Peppas order release kinetics.

Application of release rate kinetics to dissolution data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

CONCLUSION

The aim of the present study was to develop buccal formulation of buprenorphine to maintain constant therapeutic levels of the drug

for over 12 h. various grades of HPMC were employed as polymers. Buprenorphine dose was fixed as 8 mg. Total weight of the tablet was considered as 100 mg. Polymers were used in the concentration of 4 mg, 8mg and 12 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F8) showed better and desired drug release pattern i.e.,98.54 % in 12 h. It followed Peppas release kinetics mechanism.

Competing interest statement

All authors declare that there is no conflict of interests regarding publication of this paper.

Ethical approval

Not required.

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