

Design and Development of Tolperisone HCl and Diclofenac Sodium Sustained Release Tablet

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Abstract

The aim of this study was to prepare sustained release bilayer tablet of Tolperisone HCl (TOL) and Diclofenac sodium (DFS) for the effective treatment of patient with acute musculoskeletal spasm or acute low back pain. TOL and DFS were formulated as both sustained release layer by using Methocel K100M. A hydrophilic matrix-based bilayer tablet using different contents of Methocel was developed using wet granulation technique to contain 450 mg of TOL and 100 mg of DFS. The effect of contents of hydrophilic matrix (Methocel) and channel forming agent (Lactose) on TOL release was studied. The dissolution study of sustained release layer showed that an increasing amount of Methocel results in reduced TOL release. The dissolution study of sustained release layer showed that an increasing amount of lactose results in increase TOL release. The inclusion of channel forming agent (Lactose) enhanced the release of TOL from sustained release layer. Thus sustained release bilayer tablets could be a potential dosage form for delivering TOL and DFS in a controlled release manner. Formulation containing 25 mg of Methocel K100 M (DFS) and 125 mg of Methocel K100 M (TOL) in both sustained release layer showed desired drug release. Bilayer tablet was suitable for preventing direct contact of these two drugs and thus to maximize the efficacy of combination of two drugs for patient with acute musculoskeletal spasm or acute low back pain.

Keywords: Tolperisone HCl; Diclofenac sodium; Sustained release; Bilayer tablets; Methocel; Wet granulation

Introduction

Tolperisone HCl (TOL) is a centrally acting muscle relaxant which is used in the treatment of different pathological conditions like acute and chronic muscle spasm, electroconvulsive therapy, neurological conditions and orthopedic manipulation, myelopathy, encephalomyelitis, spondylosis, spondylarthrosis, cervical and lumbar syndrome, arthrosis of the large joints obliterating arteriosclerosis of the extremity vessels, diabetical anghthromboangitis obliterans, raynauds syndrome. It is recently launched drug in India for acute and chronic back pain and spasticity of neurological origin. Tolperisone hydrochloride is a "Class-I" drug according to Biopharmaceutics Classification System (BCS), possessing both high solubility and high permeability absorption characteristics. Tolperisone hydrochloride is rapidly and completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 0.9-1.0 hours after oral dosing and its elimination half-life ranges from 1.5 to 2.5 hr. TOL is official in Japanese pharmacopoeia [1,2].

DFS, or 2-[(2, 6-dichlorophenyl) amino] benzene acetic acid monosodium salt, is a NSAID having potent anti-inflammatory, analgesic, and antipyretic effects. It is an inhibitor of prostaglandin synthetase. It has an unpleasant taste and causes gastric irritation. DFS is mainly absorbed from the gastrointestinal tract. Chemically, DS is a phenyl acetic acid derivative with a pKa value of 4.0; it is practically insoluble in acidic solution but dissolves in intestinal fluid and water. The maximum average concentration in blood is between 0.7 and 1.5 mg L⁻¹ after a dose is taken. The oral bioavailability is around 60% with an excretion half life between 2.0 h. Thus, sustained release formulations are preferable to avoid frequent administration. DFS is usually prescribed as once-a-day controlled release tablets for management of painful arthritis conditions to reduce the inflammation and thereby reduce pain. Diclofenac sodium

is official in Japanese Pharmacopoeia, British Pharmacopoeia, United States Pharmacopoeia and Indian Pharmacopoeia [3,4].

An effort was made to develop simple and effective controlled release TOL and DFS bilayer tablets using a polymer matrix system with uniform *in vitro* release properties. Methocel is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems. The transport phenomena involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of Methocel exposed to water is strongly time dependent. Upon contact with the gastrointestinal fluid, Methocel swells, gels, and finally dissolves slowly. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution.

The objective of this study was to prepare sustained release bilayer tablet of Tolperisone HCl and Diclofenac sodium for the effective treatment of patient with acute musculoskeletal spasm or acute low back pain, in an attempt to improve bioavailability and to get maximum therapeutic benefits and applicable for long term therapy with better patient compliance about the treatment [5,6].

Materials and Methods

Materials

Tolperisone HCl and Diclofenac sodium were generously provided as gift sample from Themis Medicare Ltd. Vapi, India. Methocel (Methocel K4 M, Methocel K15 M and Methocel K100 M Premium grade) was obtained from Colorcon Asia Pvt. Ltd., Goa, India. Lactose was received as a gift sample from Finar Chemicals Ltd., Ahmedabad, India. Magnesium stearate and Aerosil were obtained from Acme Chemicals Ltd., Mumbai, India. All other chemicals/reagents used were of analytical grade.

Experimental Methods

Preparation of tolperisone HCl sustained release layer 1

Different tablet formulations were prepared by wet granulation technique (Table 1). All the powders were passed through a sieve of 80 mesh size. Required quantities of Tolperisone HCl, different viscosity grades Methocel and lactose were mixed thoroughly and a sufficient volume of granulating agent distilled water was added slowly. After enough cohesiveness was obtained, the mass was sieved through sieve #20. The wet mass was passed through sieve #20 and granular material was dried in oven for 1.0 hr at 40-45°C. Once dry, the granules retained on sieve #40 were mixed with 10% of fines (granules that passed through sieve #40). Aerosil and magnesium stearate were finally added as glidant and lubricant respectively. Prior to the compression, the granules were evaluated for several tests.

Preparation of optimized Diclofenac Sodium sustained release layer 2

Different tablet formulations were prepared by wet granulation technique (Table 2). All the powders were passed through a sieve of 80 mesh size. Required quantities of Diclofenac Sodium, Methocel K100M and lactose were mixed thoroughly and a sufficient volume of granulating agent distilled water was added slowly. After enough cohesiveness was obtained, the mass was sieved through sieve #20. The wet mass was passed through sieve #20 and granular material was dried in oven for 1.0 hr at 40-45°C. Once dry, the granules retained on sieve #40 were mixed with 10% of fines (granules that passed through sieve #40). Aerosil and magnesium stearate were finally added as glidant and lubricant respectively. Prior to the compression, the granules were evaluated for several tests.

The formulation “D” retains integrity and considered as optimized level of Sustained Release layer of Diclofenac Sodium for the development of bilayer tablet.

Preparation of bilayer tablets

Granules of Tolperisone HCl blend were first introduced into the die cavity, a slight compression was made and then Diclofenac Sodium blend was introduced into the die cavity followed by final compressed on 10 station rotary tablet machine using caplet punches (18 cm × 9 cm) with optimum hardness to form the bi layer tablets. The tablets were compressed to obtain hardness in a range of 6-7 Kg/cm². Bilayer tablets were prepared & evaluated for various post compression parameters and *in vitro* dissolution (Table 3) [7].

Ingredients (mg)	FORMULATION BATCH CODE								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
Tolperisone HCl	450	450	450	450	450	450	450	450	450
Methocel K100M	75	75	75	100	100	100	125	125	125
Lactose	10	20	30	10	20	30	10	20	30
Aerosil	6	6	6	6	6	6	6	6	6
Mg. Stearate	6	6	6	6	6	6	6	6	6
Total Weight	547	557	567	572	582	592	597	607	617

Table 1: Composition of Tolperisone HCl Sustained Release Layer 1

Ingredients (mg)	FORMULATION CODE	
	D	
Diclofenac Sodium	100	
Methocel K100M	25	
Lactose	71	
Aerosil	2	
Mg. Stearate	2	
Total Weight	200	

Table 2: Composition of Diclofenac Sodium Sustained Release Layer 2

Ingredients (mg)	FORMULATION BATCH CODE								
	TD1	TD2	TD3	TD4	TD5	TD6	TD7	TD8	TD9
Tolperisone HCl	450	450	450	450	450	450	450	450	450
Methocel K100M	75	75	75	100	100	100	125	125	125
Lactose	10	20	30	10	20	30	10	20	30
Aerosil	6	6	6	6	6	6	6	6	6
Mg. Stearate	6	6	6	6	6	6	6	6	6
'D' Layer	200	200	200	200	200	200	200	200	200
Total Weight	747	757	767	772	782	792	797	807	817

Table 3: Formulation of Bilayer Tablet

Drug excipient compatibility studies

Fourier-transformed infrared (FT-IR) spectroscopic studies were performed to check the compatibility between drug and polymer in formulations. The FT-IR spectra of drug alone and with formulation polymers were obtained by KBr (Potassium Bromide) disk method and compared with the standard FT-IR spectrum of the pure drug.

Characterization of granules

Prior to compression granules were evaluated for the flow properties, such as bulk density, tapped density, carr's index, Hausner ratio and angle of repose [8,9].

Evaluation of bilayer tablets

The prepared matrix tablets were evaluated for hardness, weight variation, friability, drug content, *in vitro* drug release studies. Hardness of the tablets was tested using Rimek-K-DHT 100. Friability of the tablets was tested using Roche friabilator (Electrolab EF-2-USP). The thickness of the tablets was tested using vernier caliper (Mitutoyo CD-6, Japan). Weight variation test was performed according to I.P pharmacopoeia.

Drug content

The 20 tablets were crushed in mortar and the powder equivalent to 450 mg Tolperisone HCl and 100 mg Diclofenac sodium was transferred to 100 ml of 6.8 pH phosphate buffer in volumetric flask and filter through 0.45 µm Whatman filter paper. After necessary dilution, sample was measured at 276 nm for Diclofenac sodium and 261 nm for Tolperisone HCl using double beam UV-Vis spectrophotometer. The content of drug was calculated from simultaneous equation method [10,11].

In vitro drug release studies

The *In vitro* drug release study for the prepared bilayer tablets were conducted for period of 24 hours using eight-station USP 24 type II (paddle type) Electrolab TDL-08L dissolution test apparatus. The 700 ml of 0.1 N HCl was used as dissolution media for 2 hours followed by 22 hours 6.8 pH by adding 200 ml of 0.2 mol/L tri-basic sodium phosphate in dissolution media. Temperature was maintained constant at 37°C ± 0.5°C. The stirring speed was kept at 50 rpm. 10 ml of sample was withdrawn at specified time intervals, suitably diluted and filtered through whatman filter paper (0.45 µ size). The volume of the dissolution fluid was adjusted by replacing 10 ml of suitable dissolution medium after each sampling. The samples were analyzed by UV spectrophotometer (Shimadzu 1800, Japan) after suitable dilution at specified wavelengths (For 0.1N HCl at 269 nm for Diclofenac sodium and 261.60 nm for Tolperisone HCl, and For 6.8 pH at 276 nm for Diclofenac sodium and 261 nm for Tolperisone HCl). The amount of drug present in each sample was calculated with the help of appropriate simultaneous calibration curve and compared with reference standard [12].

Release kinetics

The rate and mechanism of *in vitro* drug release from prepared bilayer tablets was analyzed by fitting dissolution data into Zero-order (cumulative amount of drug release versus time), First-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models [13-15].

Accelerated stability studies

Optimized bilayer tablets were stored at $40 \pm 2^\circ\text{C}$ and 75% RH in a programmable environmental test chamber (Remi Instruments, Mumbai, India). The bilayer tablets were withdrawn at 1, 2, and 3 month time intervals and evaluated for post-compression parameters like friability, hardness, drug content and *in vitro* drug release.

Result and Discussion

Drug excipients compatibility study

The FTIR scan was recorded by using FTIR spectrometer Shimadzu (8400 S) using KBr as negative control (blank). The sample was then analysed at a scanning range $400\text{-}4000\text{ cm}^{-1}$. The interaction study of Tolperisone HCl and Diclofenac sodium with the polymer used was studied using Fourier Transform Infrared spectroscopy method. FT-IR spectra of pure drugs and formulation were measured using FT-IR instrument by KBr mixing method. It was found that there were no changes in these main peaks in the FTIR spectra of a mixture of drugs and polymer. Hence, it was concluded that drug had not any interaction with the polymers as revealed from Figure 1 and Tables 4 and 5.

Characterization of granules

From the values of bulk densities of the formulation indicated good packing character. Bulk and tapped density observed for all formulations (T1-T9, D) was in the range $0.360\text{-}0.464\text{ g/ml}$ and $0.413\text{-}0.528\text{ g/ml}$ respectively. The angle of repose was observed in the range $26^\circ.80'$ to $29^\circ.57'$. Carr's index was varied in the ranges of 9.70% to 13.33% indicating that the granular blend has good flow property and excellent compressibility for all formulation, and Hausner ratio in the range 1.10-1.15 (Table 6). Results showed that all parameters were within limits.

Evaluation of bilayer tablet

The parameters of the bilayer tablets (batches TD1-TD9) such as weight variation, hardness, friability, and drug content were checked and are represented in Table 7. Weight variation of the bilayer tablet was found to be within limits ($100 \pm 5\%$). Friability of the bilayer tablet ($0.51\text{-}0.64\%$)

Functional Group	Frequency of Pure Drug (cm^{-1})
C=O amide	1676.20
C-N stretch	1450.52
C-N stretch	1327.07
Alkenes C-H bending	972.16
Alkenes C-H bending	837.13
Aromatic C-H bending	750.33

Table 4: Functional group and frequency of pure Tolperisone HCl

Functional Group	Frequency of Pure Drug (cm^{-1})
N-H stretch	3259.81
C-N stretch	1284.63
C=N bend	1573.97
Disubstituted aromatic ring	748.41
C-O-C bend	1305.85

Table 5: Functional group and frequency of Pure Diclofenac sodium

Batch code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's Ratio	Carr's Index (%)	Angle of repose ($^\circ$)
T1	0.375	0.428	1.14	12.38	28.73
T2	0.390	0.450	1.15	13.33	27.75
T3	0.387	0.428	1.10	9.70	26.80
T4	0.362	0.413	1.14	12.34	28.73
T5	0.377	0.428	1.13	12.01	28.01
T6	0.400	0.444	1.11	9.99	28.73
T7	0.360	0.413	1.14	12.83	27.21
T8	0.370	0.416	1.12	11.05	29.57
T9	0.362	0.413	1.14	12.34	28.73
D	0.464	0.528	1.12	11.64	28.99

Table 6: Characterization of Granules

was found to be less than 1%. Hardness was found to be 6.7 ± 0.12 to $6.9 \pm 0.27\text{ kg/cm}^2$, and drug Content of DFS and TOL in the bilayer tablet was found to be 98.25 ± 0.12 to 101.50 ± 0.28 and 98.17 ± 0.24 to 101.11 ± 0.12 , respectively.

In vitro drug release

The formulations containing the higher content of the polymer shows higher drug release time compare to formulation containing lesser content of polymer. Increase in the content of Lactose increase the channel formation in the tablet shows decrease the drug release time.

To study the effect of polymer content on drug release, nine different formulations for each drug, having different content of Methocel K100 M and channeling agent lactose, were developed. Figure 2 shows the effect of different content of Methocel K100 M and lactose; 75/10, 75/20, 75/30, 100/10, 100/20, 100/30, 125/10, 125/20 and 125/30 (% w/w of Methocel K100 M/lactose) on release rate of Tolperisone HCl. The results of *in vitro* drug release study are depicted in Table 8 and Figure 2.

All batches exhibits initial burst release of drug due to rapid dissolution of drug from tablet surface. Formulation batch T7 shows 100.27% drug release at the end of 23 hrs. Finally, Dissolution data for optimized Diclofenac sodium layer is given in Table 8 and Figure 2. All the bilayer tablets contains Diclofenac sodium layer were given good release profile. In formulation batches TD1 to TD9, average of Diclofenac sodium layer was given 101.38% drug release at the end of 22 hrs.

Kinetic treatment of dissolution profiles

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to Korsmeyer et al. [15] equation as

$$Mt / M_\infty = Kt^n$$

Where, Mt/M_∞ = fraction solute release; t =release time; K =kinetic constant characteristic of the drug/ polymer system; n = exponent that characterizes the mechanism of release of traces.

Based on various mathematical models, the magnitude of the release exponent "n" indicates the release mechanism (i.e. non Fickian diffusion or anomalous transport). In the present study value of n between 0.45 and 0.85 which indicate non fickian diffusion mechanism or anomalous transport. All the formulations revealed Korsmeyer peppas model for the drug release (Table 9).

Statistical analysis of factorial batches of tolperisone HCL layer

The 3^2 factorial design was selected to study the effect of independent variables Methocel100M (X1) and Lactose (X2) on dependent variables t_{50} and t_{90} indicates time required to release 50% of drug and 90% of drug respectively, $Q_1, Q_{12}, Q_{18}, Q_{22}$, and diffusion exponent (n). The fitted regression equations relating the responses t_{50} and $t_{90}, Q_1, Q_{12}, Q_{18}, Q_{22}$ and diffusion exponent (n) are shown in the following equations respectively.

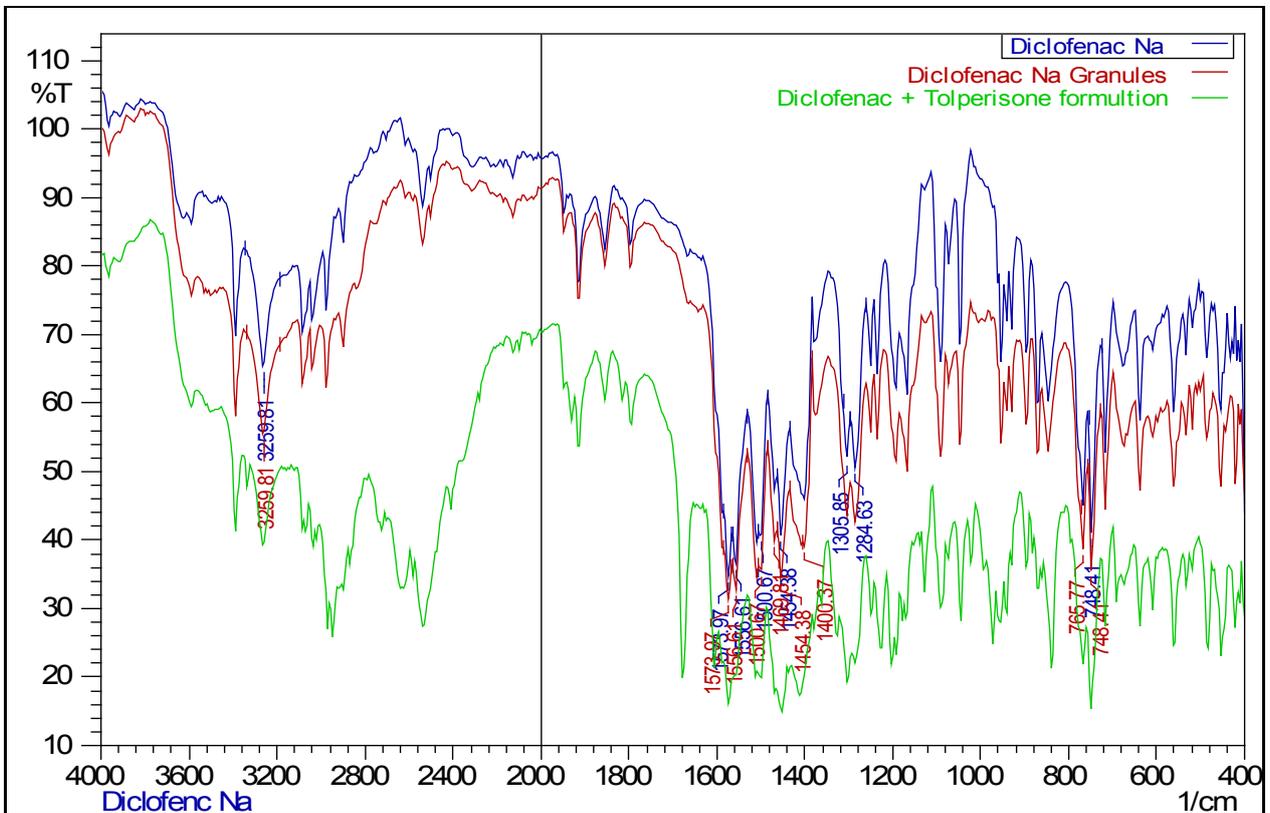
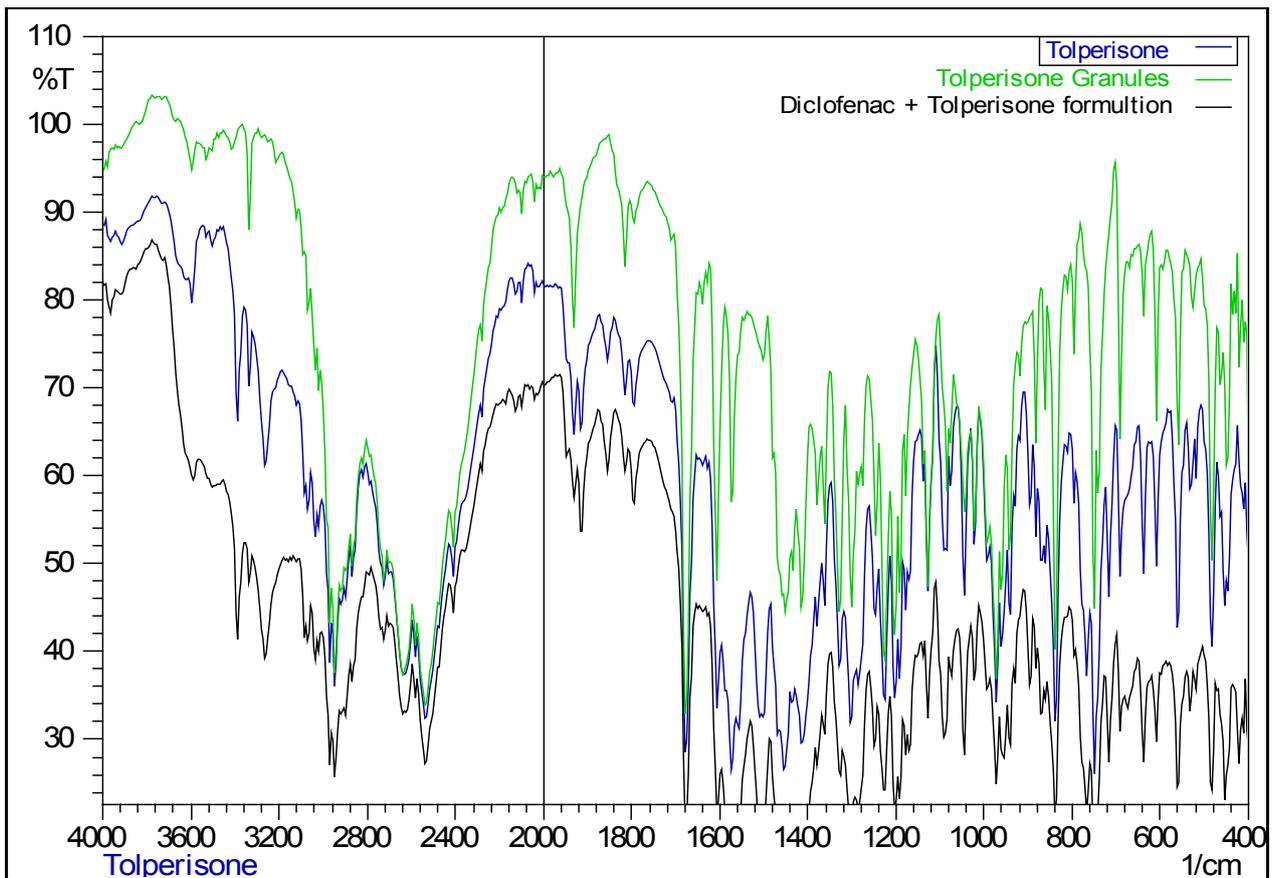


Figure 1: FTIR spectrum of Bilayer Tablet formulation

Batch Code	Weight Variation (mg) ± S.D (n=20)	Hardness* (Kg/cm ²) ± S.D	Friability (%)	Drug Content* (%) ± S.D	
				Diclofenac sodium	Tolperisone HCl
TD1	746 ± 1.22	6.7 ± 0.12	0.59	98.25 ± 0.12	99.83 ± 0.27
TD2	755 ± 1.29	6.8 ± 0.15	0.60	99.25 ± 0.15	99.78 ± 0.35
TD3	764 ± 1.35	6.7 ± 0.17	0.58	100.25 ± 0.13	100.83 ± 0.25
TD4	773 ± 1.36	6.9 ± 0.25	0.64	98.75 ± 0.26	99.56 ± 0.19
TD5	779 ± 1.21	6.9 ± 0.21	0.51	99.75 ± 0.31	98.72 ± 0.33
TD6	788 ± 1.43	6.8 ± 0.22	0.53	98.25 ± 0.43	98.17 ± 0.24
TD7	799 ± 1.36	6.9 ± 0.27	0.56	99.50 ± 0.20	99.67 ± 0.23
TD8	805 ± 1.89	6.9 ± 0.26	0.63	101.50 ± 0.28	99.83 ± 0.25
TD9	818 ± 1.18	6.8 ± 0.18	0.58	98 ± 0.32	101.11 ± 0.12

Table 7: Evaluation of Bilayer Tablet

Time (Hr)	Cumulative percentage drug release (CPR)									
	T1	T2	T3	T4	T5	T6	T7	T8	T9	DFS (Avg.)
0	0	0	0	0	0	0	0	0	0	0
1	16.02	16.89	17.68	15.23	16.11	16.98	15.15	15.32	15.93	11.01
2	21.85	21.08	23.62	21.05	21.16	21.95	18.43	19.22	20.19	14.76
4	31.78	36.30	37.45	30.03	31.15	32.39	24.83	27.05	28.06	24.77
6	42.05	48.13	49.58	39.28	39.32	43.16	31.77	32.57	34.58	32.79
8	54.39	59.72	61.48	46.53	48.04	53.30	40.08	41.02	43.92	41.08
10	66.47	72.29	76.29	56.86	57.91	62.44	46.46	47.43	51.36	47.36
12	80.64	86.21	91.51	66.65	69.32	71.74	53.83	55.91	57.85	55.04
13	87.59	93.31	100.88	71.49	74.92	77.12	57.44	59.30	61.02	57.82
14	94.48	100.40	-	77.48	79.00	85.61	60.72	63.22	65.92	61.53
15	99.98	-	-	81.22	85.80	93.46	64.28	67.41	70.51	66.98
16	-	-	-	87.91	93.64	101.26	69.58	71.29	74.90	73.44
17	-	-	-	93.82	100.46	-	72.25	74.22	78.60	78.92
18	-	-	-	99.78	-	-	76.16	79.48	83.42	84.00
19	-	-	-	-	-	-	81.69	84.32	88.54	88.85
20	-	-	-	-	-	-	86.05	89.56	95.29	93.93
21	-	-	-	-	-	-	90.94	93.75	102.34	97.29
22	-	-	-	-	-	-	96.11	99.44	-	101.38
23	-	-	-	-	-	-	100.27	-	-	-

*Standard deviation values of all the batches are within limit ± 2% (n=3)

*Diclofenac sodium (DFS) average CPR for TD1 to TD9 batches

Table 8: Cumulative percentage drug release of bilayer tablets of batches TD1-TD9

Equations:

$$t_{50} = 7.895 + 1.88 (X_1) - 0.513 (X_2) + 0.436 (X_1X_2) - 0.043 (X_2X_2) - 0.010 (X_1X_2)$$

$$t_{90} = 15.794 + 3.83 (X_1) - 0.876 (X_2) + 0.793 (X_1X_1) - 0.086 (X_2X_2) - 0.010 (X_1X_2)$$

$$Q_1 = 16.0677 - 0.698 (X_1) + 0.698 (X_2) + 0.058 (X_1X_1) + 0.058 (X_2X_2) - 0.22 (X_1X_2)$$

$$Q_{12} = 69.31 - 15.128 (X_1) + 3.33 (X_2) + 1.755 (X_1X_1) - 0.11 (X_2X_2) - 1.712 (X_1X_2)$$

$$Q_{18} = 100.41 - 10.366 (X_1) + 1.606 (X_2) - 10.446 (X_1X_1) + 0.133 (X_2X_2) + 1.59 (X_1X_2)$$

$$Q_{22} = 100.30 - 0.561 (X_1) + 1.268 (X_2) - 0.308 (X_1X_1) - 0.208 (X_2X_2) + 1.332 (X_1X_2)$$

$$n = 0.660 + 0.0074 (X_1) - 0.013 (X_2) - 0.013 (X_1X_1) - 0.0004 (X_2X_2) + 0.009 (X_1X_2)$$

The t_{50} and t_{90} , Q_1 , Q_{12} , Q_{18} , Q_{22} and diffusion exponent (n) response for the nine batches (T1-T9) showed a wide variation in (Table 10). The coefficients of Methocel K100M and Lactose were found to be significant at $p < 0.05$ accept Q_{22} , hence confirmed the significant effect of both the variables on the selected responses.

The response surface plots (Tolperisone HCl layer) were generated using statistica software Version 8.5 to observe the effect of independent variables on the response studied such as t_{50} , t_{90} , Q_1 , Q_{12} , Q_{18} , Q_{22} , and n, respectively. The response surface plots revealed that various combinations of independent variables Methocel K100 M (X_1) and Lactose (X_2) may satisfy any specific requirement while taking into consideration of various factors involved in dosage form (Figures 3 to 9).

Stability study of the optimized bilayer tablet

The optimized formulation (TD7) was selected, packed in aluminium foil and subjected to stability studies as per ICH guidelines, $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH (Humidity control oven). Samples were withdrawn at time intervals of 1, 2 and 3 month.

The samples were evaluated for hardness, friability, assay and in vitro release profile. The results revealed no significant change in the parameters. The studies revealed that TD7 formulation is stable (Table 11).

The results of hardness, friability and drug content of the formulations subjected to stability studies and in vitro drug release depicted in (Table 11). The drug content and *in vitro* drug release versus time profile showed a no significant difference in % drug content and % drug release after 3 month when compared with initial.

Summary and Conclusion

The use of polymeric matrix devices to control the release of variety of therapeutic agents has become increasingly important in development of the sustained release dosage forms. The device may be a swellable, hydrophilic monolithic systems, an erosion controlled monolithic system or a non erodible system. The present investigation endeavoured to develop the once a day Tolperisone HCl and Diclofenac sodium bilayer tablet using the Methocel as matrix forming material and lactose as channel forming

Formulation code	Zero order		First order		Higuchi		Korsmeyer and Peppas	
	R ²	S	R ²	S	R ²	S	R ²	n
T1	0.944	4.040	0.903	0.030	0.971	26.137	0.985	0.663
T2	0.929	3.886	0.879	0.029	0.966	25.423	0.984	0.640
T3	0.915	3.786	0.868	0.028	0.959	24.940	0.981	0.615
T4	0.982	4.104	0.944	0.033	0.985	25.871	0.991	0.669
T5	0.975	4.141	0.940	0.032	0.981	26.197	0.989	0.663
T6	0.966	4.093	0.926	0.031	0.980	26.122	0.989	0.648
T7	0.998	3.815	0.978	0.034	0.977	23.467	0.982	0.660
T8	0.998	3.851	0.976	0.033	0.979	23.747	0.984	0.651
T9	0.997	4.016	0.973	0.033	0.979	24.801	0.985	0.651

S= slope, R²= square of correlation coefficient, n= diffusion exponent

Table 9: Kinetics of Drug Release for Formulation Batches

Batch Code	Response						
	t ₅₀	t ₉₀	Q ₁	Q ₁₂	Q ₁₈	Q ₂₂	n
T1	6.98	13.60	16.02	80.64	99.98	99.98	0.663
T2	6.35	12.62	16.89	86.21	100.40	100.40	0.640
T3	5.94	11.88	17.68	91.51	100.88	100.88	0.615
T4	8.30	16.58	15.23	66.65	99.78	99.78	0.669
T5	7.96	15.83	16.11	69.32	100.46	100.46	0.663
T6	7.34	14.80	16.98	71.74	101.26	100.26	0.648
T7	10.69	21.16	15.15	53.83	76.16	96.11	0.660
T8	10.25	20.52	15.32	55.91	79.48	99.44	0.651
T9	9.61	19.40	15.93	57.85	83.42	102.34	0.651

t₅₀ and t₉₀ indicate time required for 50% and 90% drug release respectively, Q₁, Q₁₂, Q₁₈, Q₂₂, n indicate percentage drug release after 1st hr, 12nd hr, 18th hr Q₂₂nd and diffusion exponent respectively.

Table 10: Result of dependent variables

Parameter	Initial	After 1 month	After 2 months	After 3 months	
Hardness (kg/cm ²)	6.9	6.8	6.8	6.8	
Friability (%)	0.56	0.58	0.57	0.57	
Drug Content (%)	Tolperisone HCl	99.67	99.61	99.54	99.50
	Diclofenac sodium	99.50	99.25	99.21	99.15
% Drug Release	Tolperisone HCl	100.27 for 23 hr	-	-	98.92 for 23 hr
	Diclofenac sodium	101.38 for 22 hr	-	-	99.65 for 22 hr

Table 11: Result of bilayer tablets parameter of Accelerated Stability Study

agent. The tablets formed by using wet granulation process displayed appreciable retardation in the drug release. The channelling agent was incorporated into the controlled release system to alter porosity and drug release. In the lactose containing bilayer drug release was achieved due to dissolution of lactose and formation of channels in the matrix that allows the dissolution and diffusion of the drug. 3² full factorial design was employed to study the effect of proportion of Methocel K100 M (X₁) and proportion of channelling agent lactose (X₂) on independent variable, time required for drug release 50% (t₅₀), time required for drug release 90% (t₉₀), percentage drug release at 1, 12, 18, 22 hours and diffusion exponent (n) showed extensive deviation.

Drug excipient compatibility was studied by FT-IR spectral analysis, the results revealed that there were no interactions between drugs and excipients in this investigation for the development of the bilayer tablet formulation. The drug content was uniform in all the formulation of the bilayer tablets prepared. Pre compression and post compression parameters for all the bilayered tablets formulations were evaluated and the results obtained were satisfactory limits. Methocel K100 M retards the drug release more as compared to Methocel K4 M and Methocel K15 M. The polymer concentration was found to influence the release

of drug from the formulation. The result of *in vitro* drug release profile of bilayer tablets depicts that increase in polymer level, the release rates were found to be decrease. It was found that increases in the content of lactose increase the drug release rate. Fixed optimized batch for all bilayer formulation, Diclofenac sodium was found to be drug release up to 22 hr.

The content of Methocel K100 M and lactose were successfully optimized by using 3² factorial designs. The bilayer tablets of each batch

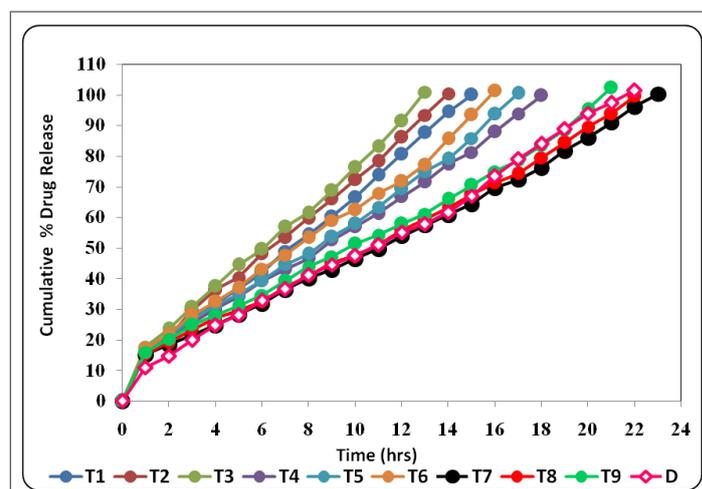


Figure 2: *In vitro* Drug release studies of Bilayer Tables of TD1-TD9

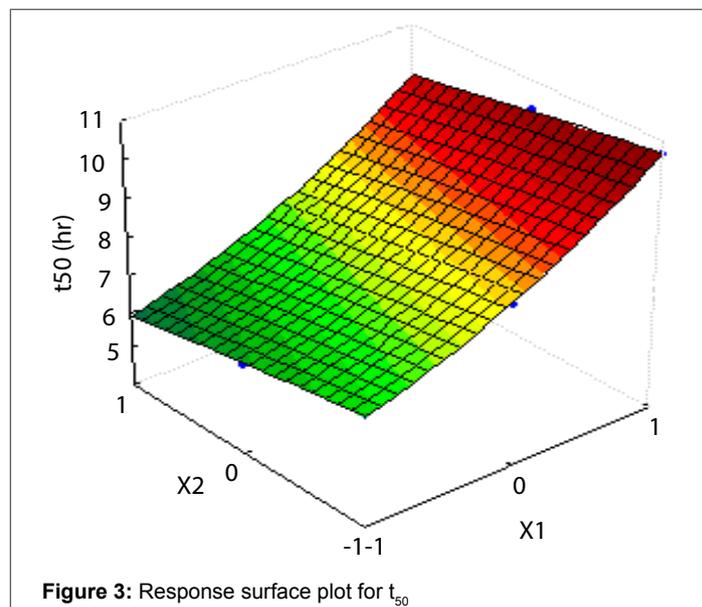


Figure 3: Response surface plot for t₅₀

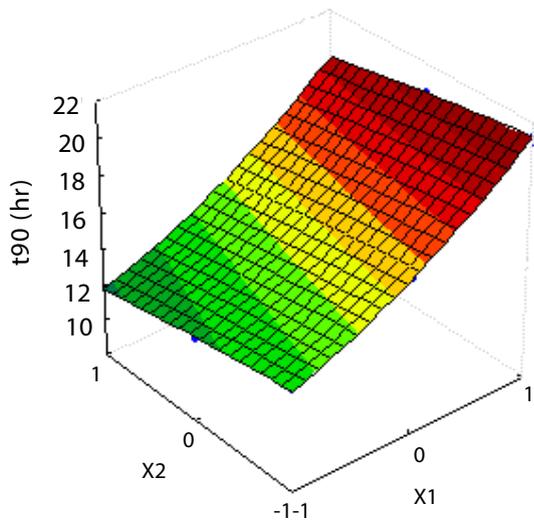


Figure 4: Response surface plot for t_{90}

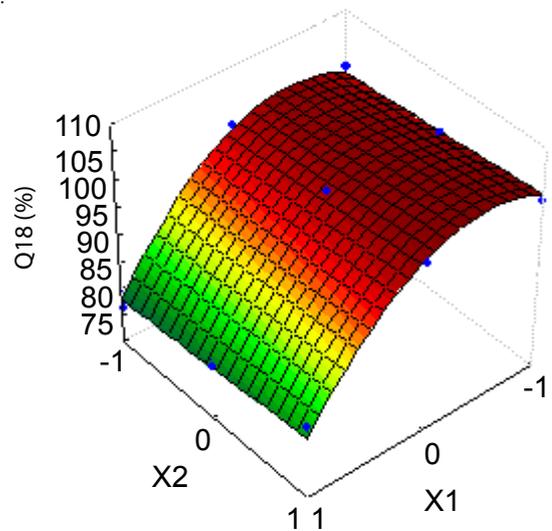


Figure 7: Response surface plot for Q_{18}

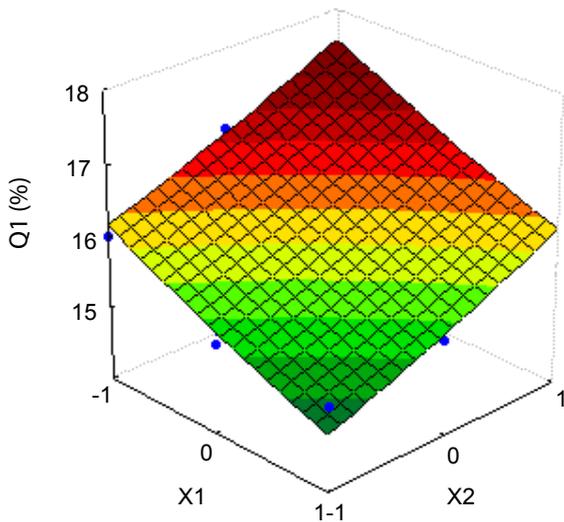


Figure 5: Response surface plot for Q_1

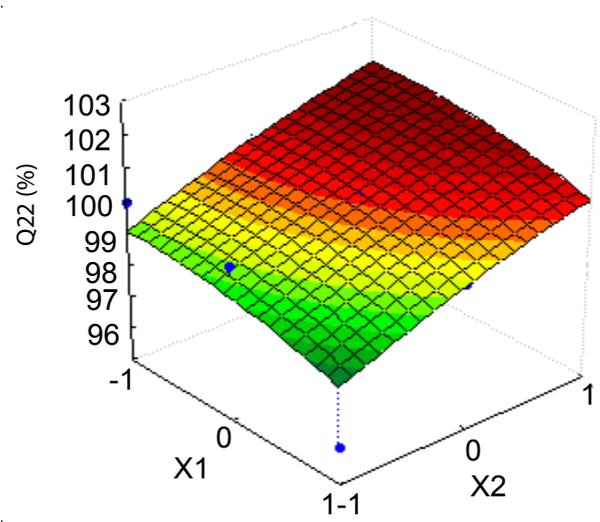


Figure 8: Response surface plot for Q_{22}

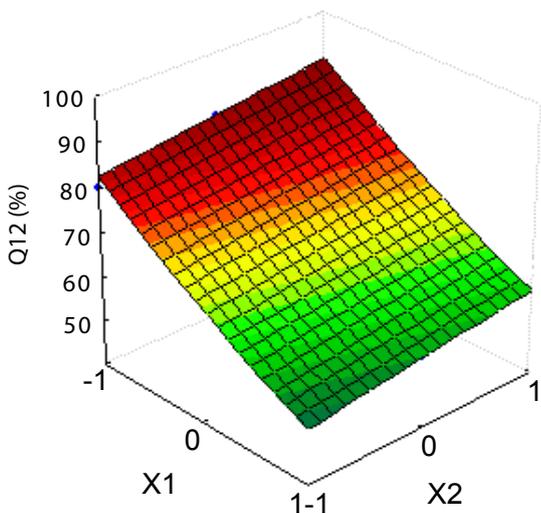


Figure 6: Response surface plot for Q_{12}

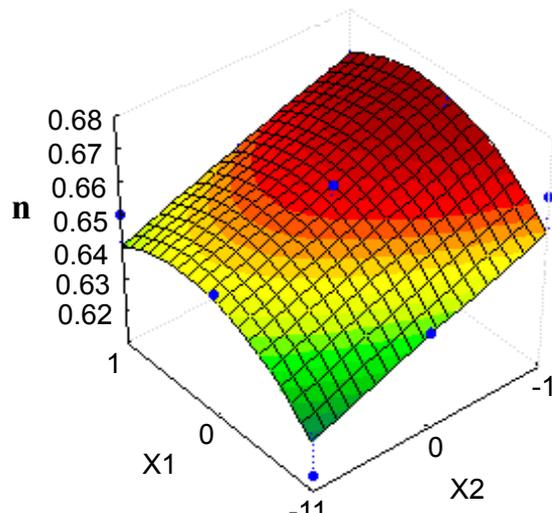


Figure 9: Response surface plot for n

had desire pre-compression and post-compression characteristics. Amongst all the batches of factorial design, batch T7 (Tolperisone HCl) have more desirable characteristics as the sustained release bilayer tablet demonstrate 100.27% release during 23 hrs release study. The value of diffusion exponent was 0.660 which indicate that the release was anomalous non fickian based and drug release during the first hours of dissolution study was 15.15%. We found that TD7 has best result and good release profile. More ever, the dissolution profile of optimized batch T7 was found to be similar with theoretical drug release profile having similarity factor more than 50 ($f_2=86.74$) and dissimilarity factor less than 15 ($f_1=2.08$) which reflects the feasibility of the optimization procedure in successful development of sustained release bilayer tablets containing Tolperisone HCl by using Methocel K100M. The bi-layer tablets showed drug release of Tolperisone HCl (upto 23 hr) and Diclofenac sodium (upto 22 h). It was observed that the optimized formulation TD7 had desired drug release kinetics and found to be stable for the period of 3 month at accelerated condition.

Our data shows that Bilayer tablets of Tolperisone HCl and Diclofenac sodium might be a suitable treatment for acute musculoskeletal spasm or acute low back pain because they allow sequential release of the two drugs.

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Declaration of Interest

The authors report no conflicts of financial interest. The authors alone are responsible for the content and writing of the paper.

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