

BILAYER TABLET TENDERED IMMEDIATE RELEASE OF PARACETAMOL AND SUSTAINED RELEASE OF IBUPROFEN FOR QUICK ONSET OF ACTION AGAINST PAIN AND FEVER

DEVENDER CHAUHAN*, DINESH KAUSHIK

Department of Hindu College of Pharmacy, Sonipat, Haryana, India. Email: devenderchauhan1112@gmail.com

Received: 15 September 2019, Revised and Accepted: 17 October 2019

ABSTRACT

Objective: The objective of this research was to formulate bi-layer tablet which contains immediate-release layer of Paracetamol for quick onset of action and sustained release of Ibuprofen for prolonging long period.

Materials and Methods: The following chemicals were used: Paracetamol (Combiotic Global Pvt. Ltd., India), Ibuprofen (Combiotic Global Pvt. Ltd., India), microcrystalline cellulose (MCC) (Avicel), and Polyvinylpyrrolidone (PVP) K-30 (Loba Chem). Wet granulation method was adapted to formulate the bilayer tablets. The immediate-release layer of Paracetamol was prepared using sodium starch glycolate as superdisintegrants, MCC as diluent, starch as binder. The sustained release layer of Ibuprofen was prepared using high-performance liquid chromatography E50LV and ethyl cellulose as binder along with other excipients such as MCC, PVP, and magnesium stearate by wet granulation technique.

Result and Discussion: The release rate of Paracetamol from Formulations 1 was more than 80% at 40 min. In case of Ibuprofen, sustained-release polymers such as HPMC E50 LV were used to increase the release time.

Conclusion: The bilayer tablets were prepared and show good release rate.

Keywords: Paracetamol, Ibuprofen, Analgesic, Immediate release, Sustained release, High-performance liquid chromatography.

© 2019 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2019.v12i11.35690>

INTRODUCTION

Oral drug delivery system is considered to be one of the most convenient and commonly employed drug delivery system as it possesses some specific advantageous characteristics, such as ease of administration [1,2]. The modified release products are usually designed to provide slow and continuous delivery of drug over the entire dosing interval and improve patient compliance and convenience [3,4]. In formulation of oral controlled release formulation, hydrophilic polymers are most frequently used as polymeric retardant materials due to their ease of manufacturing, relatively low cost, favorable *in vivo* performance, and versatility in controlling the release of drug with wide range of physicochemical properties [5-7].

Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery [8,9]. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer tablets are novel drug delivery systems where a combination of two or more drugs in a single unit [10,11]. Bi-layer tablet is suitable for sequential release of two drugs in combination in which one layer is for immediate release and second layer is sustained release. Hence, the use of bi-layer tablets is a very different aspect for anti-inflammatory, analgesic, diabetic, and anti-hypertensive drugs where combination therapy is often used [12,13].

MATERIALS AND METHODS**Materials**

The following chemicals were used: Paracetamol (Combiotic Global Pvt. Ltd., India), Ibuprofen (Combiotic Global Pvt. Ltd., India), Microcrystalline cellulose (MCC) (Avicel), Polyvinylpyrrolidone (PVP) K-30, starch, sodium starch glycolate, IPA, HPMC, Ethanol and Ethyl cellulose (Loba Chemie), Acetonitrile (High-performance liquid chromatography [HPLC] grade), and Methanol (HPLC grade) (Merck).

Methods*Solubility study*

The solubility study of drugs was performed in water, methanol, ethanol, acetone, 0.1 N HCl, phosphate buffer pH 6.8, phosphate buffer pH 7.4, and individually by keeping the drug-containing test tube on vortex mixture.

Determination of melting point

All dynamic differential scanning calorimetry (DSC) studies of pure drugs were carried out on DSCTA 60 Shimadzu Thermal Analyzer. The instrument was calibrated using high purity indium metal as standard. The scans were taken in nitrogen atmosphere at the heating rate of 10°C/min.

Linearity and validation by HPLC method*Mobile phase preparation*

A mixture of 75 volume of a buffer solution prepared by dissolving 3.9 g of sodium dihydrogen phosphate dihydrate and 8.9 g disodium hydrogen phosphate dihydrate in water, adjust to pH 7.0 with orthophosphoric acid, dilute to 1000 ml with water and 24.5 volume of acetonitrile and 0.5 volume of methanol.

Chromatic condition

Apparatus: HPLC
Column: C8
Wave length: 220 nm
Injection volume: 20 µl
Flow rate: 1 ml/min
Column temperature: 35°C
Type of detector: UV

- Standard stock solution of Paracetamol
Accurately weighed 100 mg of Paracetamol and was dissolved in 100 ml of the mobile phase. 1 ml pipette out from above solution and taken in 10 ml volumetric flask and volume make up with mobile phase. A standard stock solution contains 100 µg/ml.

Standard graph of Paracetamol: Form this standard stock solution, a series of dilution (10, 20, 30, 40, and 50 $\mu\text{g/ml}$) were prepared using mobile phase.

- Standard stock solution of Ibuprofen
Accurately weighed 100 mg of Ibuprofen and was dissolved in 100 ml of mobile phase. 1 ml pipette out from above solution and taken

Table 1: Formulations containing Paracetamol immediate-release layer (in mgs)

Ingredients (mg)	F1	F2	F3	F4	F5
Paracetamol	325	325	325	325	325
MCC	48	48	48	48	48
Starch	32	64	-	-	48
PVP K-30	-	-	6	12	32
Sodium starch glycolate	7	7	7	7	7
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s

MCC: Microcrystalline cellulose

Table 2: Formulations containing Ibuprofen release layer (in mgs)

Ingredients (mg)	F1	F2	F3	F4	F5
Ibuprofen	400	400	400	400	400
MCC	40	40	40	40	40
HPMC E50LV	80	120	-	-	80
Ethylcellulose	-	-	30	60	30
PVP K-30	8	8	8	8	8
Magnesium stearate	5	5	5	5	5
Talc	5	5	5	5	5
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s
Erythrosine	q.s	q.s	q.s	q.s	q.s

Table 3: Comparison between peaks obtained in drug and in mixture

Peak obtained in drug (frequency cm^{-1})	Description	Peak obtained in mixture (frequency cm^{-1})
3628	OH group	3633
3441	NH group	3451
2981, 2890	C-H stretch of CH_2 , CH_2	2991, 2841
1338	C-H bending of CH_2	1310
1645	C=O stretch of amide	1648

Table 4: Area of different dilutions of Paracetamol

S. No.	Concentration ($\mu\text{g/ml}$)	Peak area
1.	0	0
2.	10	774,357
3.	20	779,816
4.	30	785,925
5.	40	791,342
6.	50	796,598

Table 5: Pre-compression parameters of Paracetamol granules

Formulation code	Angle of repose (θ) ($\pm\text{SD}$)	Bulk density (g/cc) ($\pm\text{SD}$)	Tapped density (g/cc) ($\pm\text{SD}$)	Carr's index (%) ($\pm\text{SD}$)	Hausner's ratio ($\pm\text{SD}$)
F1	25.5 \pm 0.31	0.735 \pm 0.12	0.836 \pm 0.08	14.52 \pm 0.06	1.13 \pm 0.09
F2	25.1 \pm 0.45	0.781 \pm 0.09	0.899 \pm 0.09	15.10 \pm 0.05	1.15 \pm 0.07
F3	26.3 \pm 0.98	0.782 \pm 0.08	0.902 \pm 0.08	15.34 \pm 0.08	1.15 \pm 0.09
F4	28.4 \pm 1.24	0.781 \pm 0.12	0.895 \pm 0.09	14.59 \pm 0.05	1.14 \pm 0.05
F5	28.6 \pm 0.88	0.751 \pm 0.17	0.845 \pm 0.16	14.58 \pm 0.05	1.12 \pm 0.07

(S.D=Standard deviation), n=3

in 10 ml volumetric flask and volume make up with mobile phase. A standard stock solution contains 100 $\mu\text{g/ml}$.

Standard graph of Ibuprofen: Form this standard stock solution, a series of dilution (10, 20, 30, 40, and 50 $\mu\text{g/ml}$) were prepared using the mobile phase [21].

Fourier transform infrared spectroscopy (FTIR)

The selected drug and polymers were characterized by FT-IR spectroscopy and the FTIR spectra of the pure drug Paracetamol with used excipients such as MCC, PVP K-30, starch, and sodium starch glycolate and Ibuprofen with excipients such as HPMC E50LV, ethylcellulose, PVP K-30, magnesium stearate, and talc were recorded to know the drug excipient interactions. The spectrum was recorded for pure drug, physical mixture of combination of all the excipients and drugs. The scanning range was 4000–500 cm^{-1} [15].

Formulation of bilayer tablets

The proposed bilayer tablets contain two layers.

- An immediate release layer containing Paracetamol.
- Sustained-release layer containing Ibuprofen.

Formulation of Paracetamol granules

Different formulations of immediate-release tablets of the Paracetamol layer (F1–F5) were prepared by wet granulation method using different excipients such as MCC, starch, and PVP K-30 as a binder and sodium starch glycolate were used as disintegrants.

Procedure

Appropriate quantities of Paracetamol and excipients such as MCC, Starch, PVP K-30, and sodium starch glycolate were measured accurately, and all the measured powders were sifted through Sieve no # 40. The above-sifted materials were mixed rapidly for 5 min and again passed through sieve no 40. Isopropyl alcohol having (2%) w/v amount of starch and PVP K-30 was used as the granulating solution and the solution was added to the mixture in step 2 and was kneaded for 2–5 min, then the kneaded mass was passed through sieve no # 16 to obtain the granules. The granules obtained in step 3 were dried in a tray drier at 50°C for 2 h. The dried granules were lubricated uniformly with weighed quantities of magnesium stearate. The above granules were compressed into tablets by CADMACH multi-station tablet compression machine using 19.1 \times 8.75 mm punch.

Formulation of Ibuprofen granules

Different formulations of sustained-release tablets of Ibuprofen layer (F1–F5) were prepared by wet granulation method using different excipients such as MCC, HPMC E50 LV, and ethyl cellulose used as sustained release polymer, PVP K-30 as a binder, and magnesium stearate as a lubricant.

Procedure

Appropriate quantities of Ibuprofen and excipients such as MCC, HPMC E50 LV, and Ethyl Cellulose were measured accurately, and all the measured powders were sifted through Sieve no # 40. The above-sifted materials were mixed rapidly for 5 min and again passed through sieve no 40. Isopropyl alcohol having 2% w/v amount of PVP K-30 was used

as the granulating solution and the solution was added to the mixture in step 2 and was kneaded for 2–5 min, then the kneaded mass was passed through sieve no # 16 to obtain the granules. The granules obtained in step 3 were dried in a tray drier at 50°C for 2 h. The dried granules were lubricated uniformly with weighed quantities of magnesium stearate. The above granules were compressed into tablets by CADMACH multi-station tablet compression machine using 19.1 × 18.75 mm punch.

Evaluation of granules

Angle of repose (θ)

Angle of repose is an indication of fractional forces existing between granules particles. The maximum angle possible between the surface of the pile of granules and the horizontal plane gives the angle of repose.

$$\tan(\theta) = \frac{h}{r}$$

Where (θ) = angle of repose
h = height of heap of granules
r = radius of heap

Bulk density

Bulk density of the powder is the ratio of the mass of an untapped powder sample and its volume indicating the contribution of the intra-particulate void volume. The bulk density is expressed in grams per ml (g/ml). Bulk density is determined by weighing powder into a dry graduated 250 ml cylinder. The powder was carefully leveled without compacting, volume (V_0) was recorded, and bulk density g/ml was calculated using the following formula.

$$\text{Bulk density} = \frac{\text{Mass of the Blend powder}}{\text{Volume occupied by the powder blend}}$$

Tapped density

Tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing a powder sample. After observing the initial powder volume to weight, the measuring cylinder or vessel is mechanically tapped, and volume readings are taken until little less than 1% further volume change is observed. The mechanical tapping is achieved by raising the cylinder or vessel and allowing it to drop under its own weight at specified distance. Secure the cylinder in the holder of the apparatus with weighed powder sample. Measure 100–200 taps and observe the corresponding volumes to the nearest graduated unit [16].

Table 6: Area of different dilutions of Ibuprofen

S. No.	Concentration ($\mu\text{g/ml}$)	Peak area
1.	10	1,291,267
2.	20	1,367,245
3.	30	1,459,834
4.	40	1,524,783
5.	50	1,592,643

Table 7: Pre-compression parameters of Ibuprofen granules

Formulation Code	Angle of repose (θ) (\pm SD)	Bulk density (g/cc) (\pm SD)	Tapped density (g/cc) (\pm SD)	Carr's index (%) (\pm SD)	Hausner's ratio (\pm SD)
F1	25.0 \pm 0.45	0.88 \pm 0.021	0.98 \pm 0.01	12.54 \pm 0.42	1.12 \pm 0.05
F2	25.5 \pm 0.31	0.87 \pm 0.098	0.99 \pm 0.04	11.49 \pm 0.53	1.13 \pm 0.06
F3	28.4 \pm 1.24	0.85 \pm 0.047	0.98 \pm 0.04	13.31 \pm 0.78	1.15 \pm 0.01
F4	26.3 \pm 0.98	0.86 \pm 0.047	0.99 \pm 0.04	12.50 \pm 0.44	1.14 \pm 0.05
F5	29.9 \pm 1.63	0.78 \pm 0.06	0.96 \pm 0.08	16.66 \pm 0.79	1.15 \pm 0.01

(S.D = Standard deviation), n=3

$$\text{Tapped density} = \frac{\text{Mass of the powder Blend taken}}{\text{Tapped Volume of the powder blend}}$$

Carr's index

The Carr's Index and Hausner's ratio are measures of the porosity of a powder to be compressed. They measure the relative importance of interparticle interactions. For poor flow materials, there are frequently greater interparticle interactions and a greater difference between the bulk and tapped densities. These differences are reflected in the compressibility index and Hausner's Ratio. Carr's index was calculated using the following formula.

$$\text{Carr's Index} = \frac{\text{TD} - \text{BD}}{\text{TD}} \times 100$$

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. Hausner's ratio is calculated using the following formula [17]:

$$\text{Hausner's ratio} = \frac{\text{TD}}{\text{BD}}$$

Evaluation of tablets

The formulation tablets were evaluated for the following physical parameters.

Thickness

Thickness depends on the die filling, physical properties of the material to be compared. It is possible of small variation in the thickness of individual tablets in a batch. However, it should not appear to the unaided eye. The thickness and diameter can be measured by Vernier caliper [18].

Weight variation test

Twenty tablets were selected randomly and weighed individually. Calculate average weight compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than percentage is shown in tablet and none deviate by more than twice the percentage.

Hardness

Tablets must possess sufficient strength or hardness and can be measured by Monsanto Hardness Tester. Ten tablets were randomly picked from each formulation and were evaluated for hardness and can be expressed in kg/cm².

Friability

Friability can be performed in Roche friabilator; preweighed ten tablets were introduced in the friabilator. Then, the machine was operated for 100 revolutions. Tablets were dropped from a distance of 6 in each revolution. Tablets were then dusted and reweighed. Loss of <1% in weight is considered to be within the specification and acceptable [19].

$$F (\%) = \frac{\text{Initial Weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Table 8: Post-compression parameters of bilayer tablets

Formulations code	Thickness (mm)*	Hardness (Kg/cm ²)*	Friability (%)*	Weight variation (mg)**
F1	6.5	6.8	0.59	950.33
F2	6.6	6.12	0.52	1025.68
F3	6.5	7.5	0.47	874.00
F4	6.5	7.10	0.49	915.05
F5	6.6	8.2	0.45	985.30

*All values are mean, n=3, **All values are mean, n=20

Table 9: Disintegration time for Paracetamol IR layer assay of bilayer tablets

Formulation code	Disintegration time*
F1	90-120 s
F2	4-6 min
F3	6-8 min
F4	8-10 min
F5	10-12 min

*(n=6)

Table 10: Drug content in formulation F1

Formulation code	Paracetamol	Ibuprofen
F1	97.90	97.64

Disintegration time

A tablet was placed in each of the six tubes of the basket. Suspend the assembly in water maintained at a temperature of 37°C ± 2°C and operate the apparatus, simultaneously note the time taken to disintegrate completely using stopwatch [20].

Drug content: Assay: (BY HPLC)

For Paracetamol and Ibuprofen

Procedure

Chromatographic system

Apparatus: HPLC

Column: C8

Wave length: 220 nm

Injection volume: 5 µl

Flow rate: 1.5 ml/min

Column temperature: 35°C

Type of detector: UV

Mobile phase preparation

A mixture of 75 volumes of buffer solution prepared by dissolving 3.9 g of sodium dihydrogen phosphate dihydrate and 8.9 g disodium hydrogen phosphate dihydrate in water, adjust to pH 7.0 with orthophosphoric acid, dilute to 1000 ml with water and 24.5 volume of acetonitrile and 0.5 volume of methanol.

Standard preparation

Weigh accurately 325 mg of Paracetamol into 50 ml volumetric flask and make up the volume with media. Take 2 ml from the above solution into 25 volumetric flasks and make up the volume with media.

Weigh accurately 400 mg of Ibuprofen into 50 ml volumetric flask and make up the volume with media. Take 2 ml from the above solution into 25 volumetric flasks and make up the volume with media.

Sample preparation

One tablet was taken from F1 batch and crushed in pestle mortar. Crushed powdered will be taken into 50 ml volumetric flask and make up the volume with media.

Table 11: In vitro dissolution profile of Bilayer tablets F-1

S. No.	Time intervals	Cumulative % drug release	
		Paracetamol	Ibuprofen
1.	0 min	0.00	0.00
2.	5 min	37.85	0.53
3.	10 min	72.05	2.36
4.	15 min	88.64	5.42
5.	20 min	94.20	8.37
6.	30 min	96.15	13.56
7.	40 min	97.87	19.34
8.	60 min	-	21.56
9.	2 h	-	33.75
10.	4 h	-	52.40
11.	6 h	-	71.02
12.	8 h	-	81.31
13.	10 h	-	92.20
14.	12 h	-	97.65

Table 12: Kinetics of IR drug release of formulation-1

Plot	K ₀	R ²
Zero-order	0.327	0.669
First-order	0.00460	0.933
Higuchi	9.157	0.839
Peppas	1.8156	0.843

Table 13: Kinetics of SR drug release of formulation-1

Plot	K ₀	R ²
Zero-order	0.327	0.9540
First-order	0.00460	0.9572
Higuchi	9.157	0.994
Peppas	1.8156	0.9573

Take 2 ml from the above solution into 25 volumetric flasks and make up the volume with media.

Procedure

Inject 5 µL portion of diluent as blank five replicate injections of standard preparation and one injection of each test preparation into the HPLC system record the chromatograms and measure the peaks response.

Calculation

$$= \frac{\text{Sample area}}{\text{Standard area}} \cdot \frac{\text{Standard weight}}{50} \cdot \frac{250}{25} \cdot \frac{25}{\text{Sample weight}} \cdot \frac{\text{Average weight}}{2} \cdot \frac{\text{Potency}}{\text{Labelled claim}} \cdot 100$$

In vitro dissolution studies

Procedure of dissolution of bilayer tablets

Six tablets of Paracetamol and Ibuprofen (Bilayer tablets) were introduced in the dissolution apparatus I.P Type I (paddle). The medium used was 900 ml of phosphate buffer solution (pH 5.8), and the dissolution medium was maintained at the temperature of 37.5 ± 0.5°C, the RPM was set at 50. The dissolution was carried out for 12 h and sample withdrawn at predetermined intervals. The estimation was carried out by HPLC method.

For Paracetamol and Ibuprofen

Procedure

Chromatographic system

Column: C8

Column temperature: 35°C

Flow rate: 1.5 ml/min

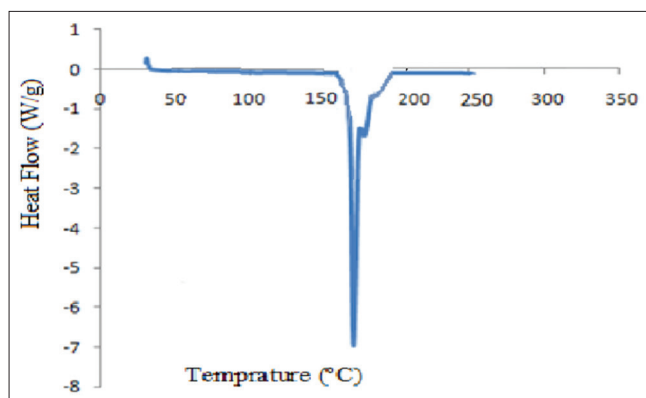


Fig. 1: Differential scanning calorimetry of Paracetamol

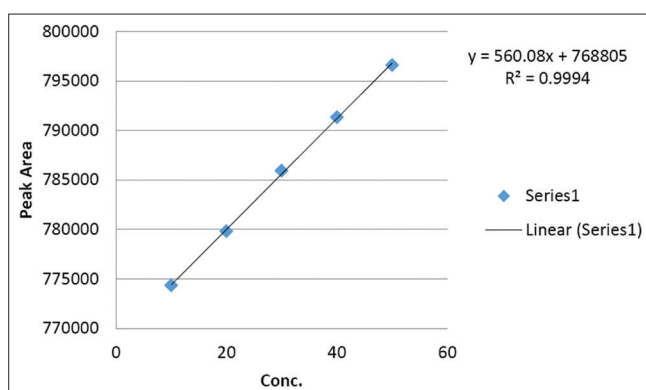


Fig. 2: Standard calibration curve of Paracetamol

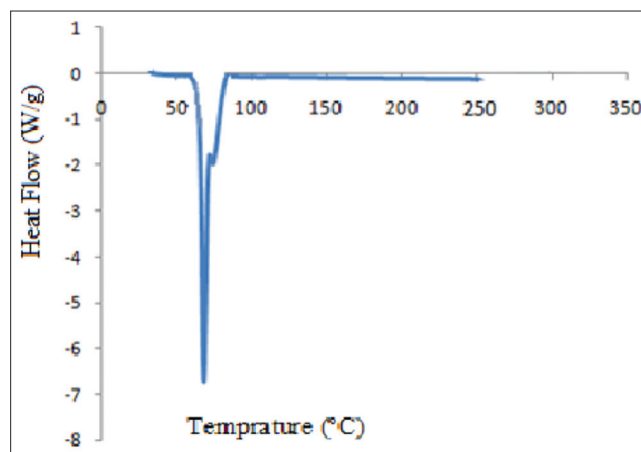


Fig. 3: Differential scanning calorimetry of Ibuprofen

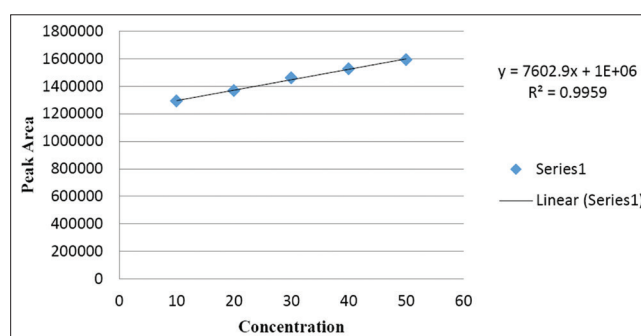


Fig. 4: Standard calibration curve of Ibuprofen

Injection volume: 5 μ l.
 Detector Wavelength: 220 nm
 Run time: 14 min
 Type of detector: UV

Dissolution media

Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 ml of water and adjust the pH to 5.8 with 0.2 M sodium hydroxide.

Mobile phase preparation

A mixture of 75 volumes of buffer solution prepared by dissolving 3.9 g of sodium dihydrogen phosphate dihydrate and 8.9 g disodium hydrogen phosphate dihydrate in water, adjust to pH 7.0 with orthophosphoric acid, dilute to 1000 ml with water, and 25 volume of acetonitrile.

Standard preparation of Paracetamol

Weigh accurately 28 mg of Paracetamol and transfer into a 100 ml volumetric flask, dissolve and dilute up to volume with dissolution media.

Take 1 ml from the above solution and transfer into 10 ml volumetric flask, dissolve and dilute up to volume with dissolution media.

Standard preparation of Ibuprofen

Weigh accurately 35 mg of Ibuprofen and transfer into a 100 ml volumetric flask, dissolve and dilute up to volume with dissolution media.

Take 1 ml from the above solution and transfer into 10 ml volumetric flask, dissolve and dilute up to volume with dissolution media.

Sample preparation

Take 2 ml from the above solution and transfer into 25 ml volumetric flask and volume make up with dissolution media.

Procedure

Inject 5 μ l portion of diluent as blank, six replicate injections of standard preparation, and one injection of each test preparation into the HPLC system, record the chromatograms, and measure the peaks response [21].

Calculation

$$= \frac{\text{Sample area}}{\text{Standard area}} \cdot \frac{\text{Standard weight}}{100} \cdot \frac{1}{10}$$

$$= \frac{900}{\text{Labeled claim}} \cdot \frac{25}{2} \cdot \frac{\text{Potency}}{100} \cdot 100$$

Drug release kinetics

The release kinetics was studied by various kinetic models such as zero-order plot, first-order plot, Higuchi plot, and Korsmeyer–Peppas plot. To study the release kinetics of the nanoparticle gel data obtained from *in vitro* drug release studies was plotted in various kinetic models: Zero-order as cumulative amount of drug releases versus time, first-order as long cumulative % of drug remaining versus time, Higuchi model as cumulative % of drug released versus square root of time, and Korsmeyer–Peppas model as log cumulative % drug release versus long time. The best fit model was confirmed by the value of correlation coefficient near to one [22].

RESULTS AND DISCUSSION

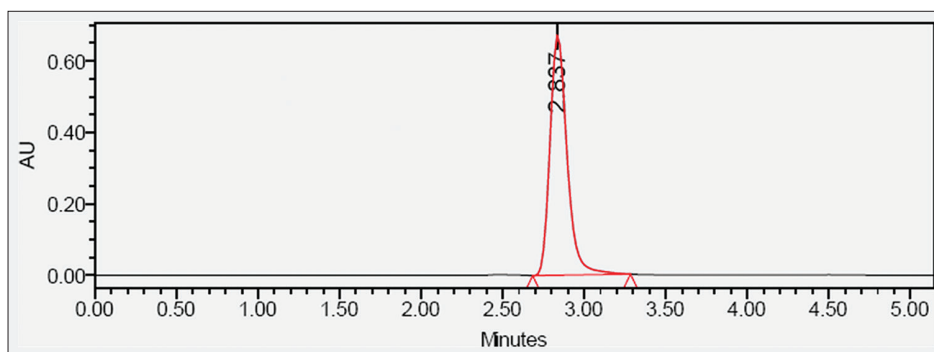
Paracetamol

Solubility

Paracetamol was found to be soluble in methanol, ethanol, acetone, 0.1 N HCL, and sparingly soluble in water.

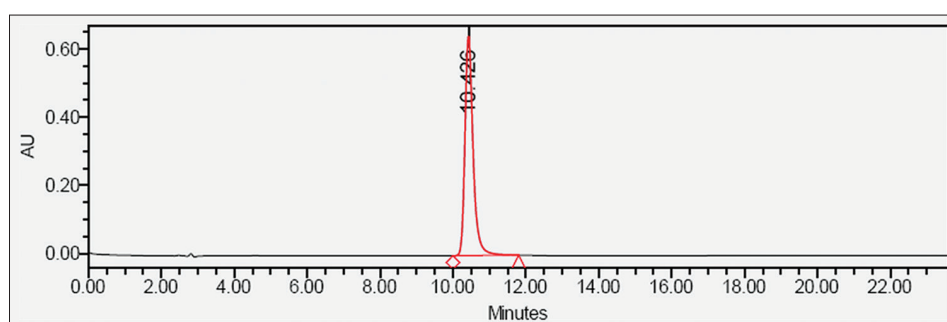
Melting point

DSC curve of Paracetamol showed a sharp endothermic peak near 169°C that is indicative of its melting temperature.



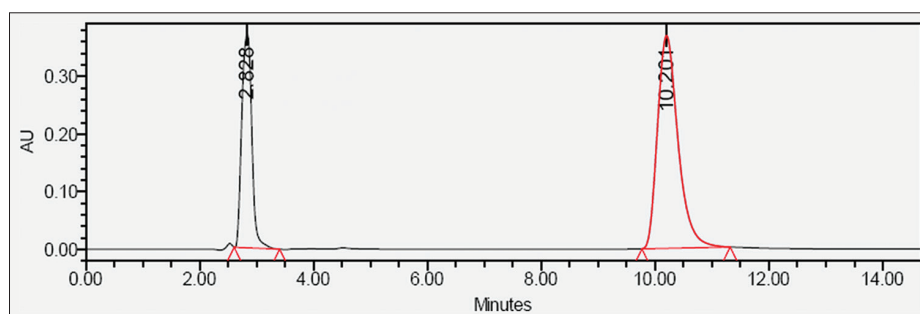
Name	Retention time	Area
Standard Paracetamol	2.837	5,645,987

Fig. 5: Paracetamol assay standard chromatogram



Name	Retention time	Area
Standard Ibuprofen	10.426	12,546,244

Fig. 6: Ibuprofen assay standard chromatogram



Name	Retention time	Area
Paracetamol	2.828	5,388,001
Ibuprofen	10.201	11,900,126

Fig. 7: Assay sample of formulation F1

FTIR analysis

FTIR spectroscopic analysis was carried out to characterize drug. The FTIR spectra obtained were compared with that given in pharmacopeia for Paracetamol. Diagnostic peaks and fingerprint regions were found identical. These characteristics peaks are useful in identification of drug. The results obtained showed that there are no interactions between the components when taken together.

Linearity by HPLC method

- Standard stock solution of Paracetamol
 Accurately weighed 100 mg Paracetamol and dissolved in 100 ml of the mobile phase. 1 ml pipette out from above solution and taken in 10 ml volumetric flask and volume was makeup with mobile phase. A standard stock solution contains 100 µg/ml.

Standard graph of Paracetamol: Form this standard stock solution, a series of dilution (10, 20, 30, 40, and 50 µg/ml) were prepared using mobile phase.

Evaluation of Paracetamol blended granules

The blended granules of different formulation were evaluated for angle of repose, bulk density, tapped density, Carr’s index, and Hausner’s ratio. The results of these evaluations were as follows:

Angle of repose

Angle of repose for the granules of F1–F5 was found to be 25.1–28.6, which indicates good flow property.

Carr’s index

The Carr's index for the granules of F1-F5 was found to be 14.58-15.34%, which shows good flowing properties.

Hausner's ratio

Hausner ratio was found to be 1.12-1.15, it indicates good flow properties of the granules.

Ibuprofen

Solubility

Ibuprofen was found to be freely soluble in methanol, ethanol, acetone, soluble in PBS of pH 6.8, 7.4, practically insoluble in water, and 0.1 N HCL.

Melting point

Melting point of the pure Ibuprofen was found to be 76°C which was within the limit as per the IP 2018. DSC curve of Ibuprofen exhibits endothermic peak at 76°C.

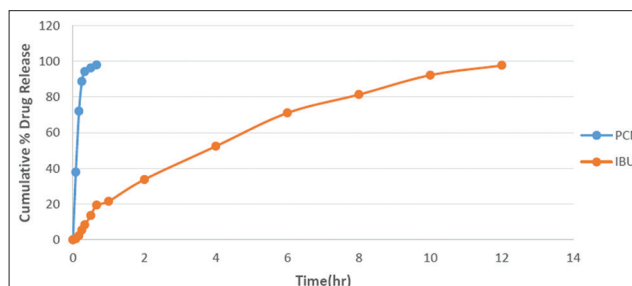


Fig. 8: In vitro dissolution profile of formulation F-1

Linearity by HPLC method

- Standard stock solution of Ibuprofen
Accurately weighed 100 mg Ibuprofen and dissolved in 100 ml of mobile phase. 1 ml pipette out from above solution and taken in 10 ml volumetric flask and volume was make up with mobile phase. A standard stock solution contains 100 µg/ml.
Standard graph of Ibuprofen: RM this standard stock solution, a series of dilution (10, 20, 30, 40, and 50 µg/ml) were prepared using mobile phase.

Evaluation of Ibuprofen blended granules

The blended granules of different formulation were evaluated for angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The results of these evaluations were as follows:

Angle of repose

Angle of repose for the granules of F1-F5 was found to be 25.0-39.9, which indicates good flow property.

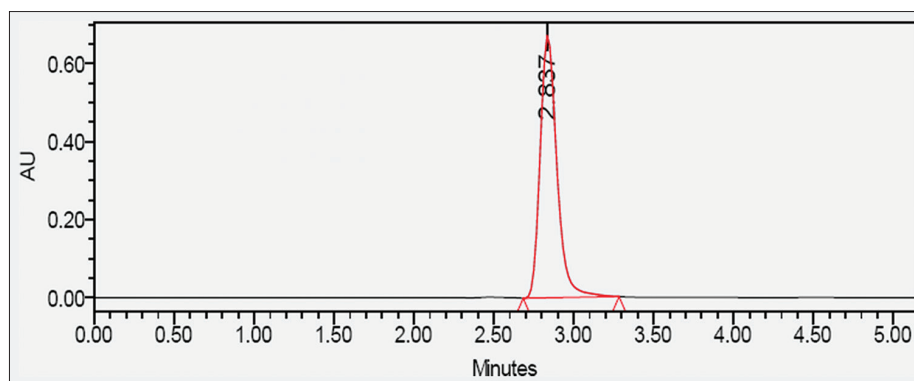
Carr's index

The Carr's index for the granules of F1-F5 was found to be 11.49-16.66%, which shows good flowing properties.

Hausner's ratio

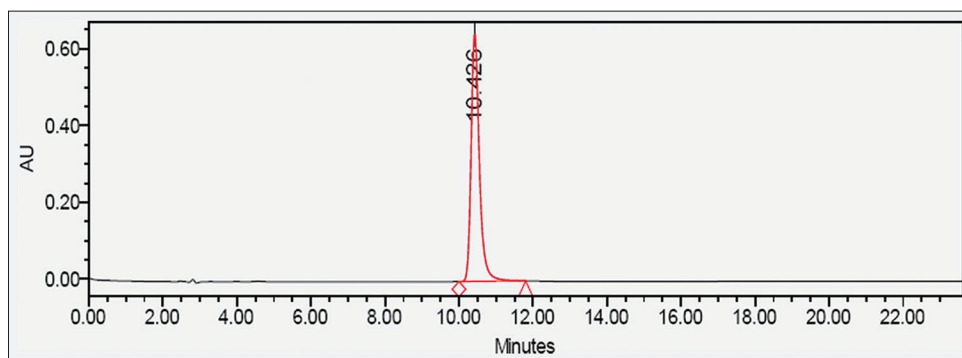
Hausner ratio was found to be 1.12-1.15; it indicates good flow properties of the granules.

Post-compression parameters



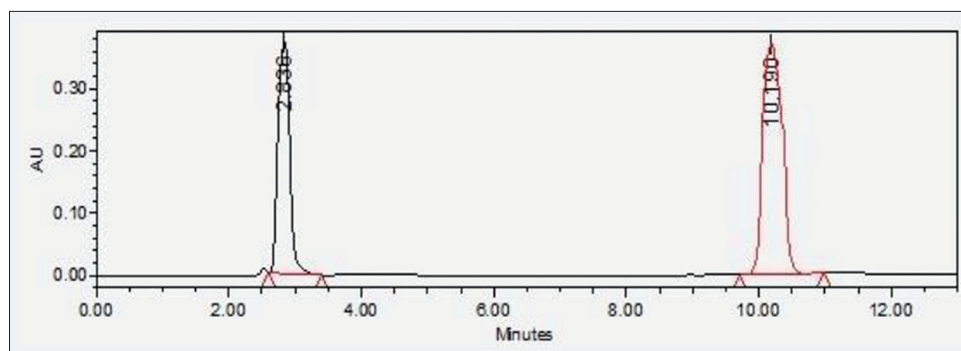
Name	Retention time	Area
Standard Paracetamol	2.837	4,899,153

Fig. 9: Dissolution standard of Paracetamol

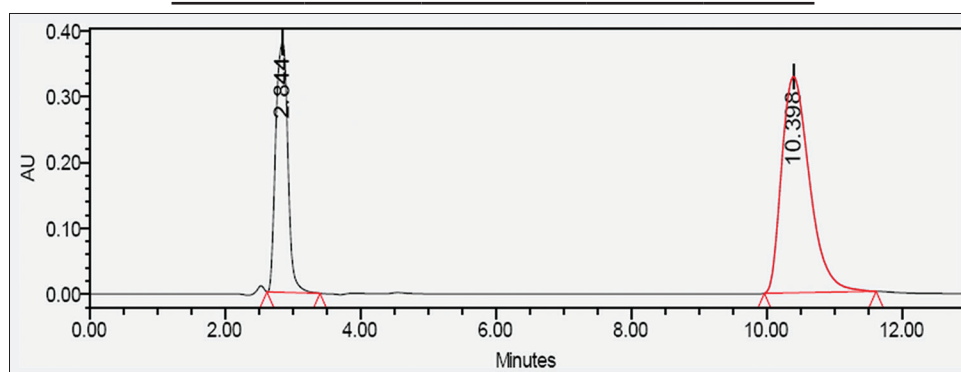


Name	Retention time	Area
Standard Ibuprofen	10.426	9,991,352

Fig. 10: Dissolution standard of Ibuprofen



Name	Retention time	Area
Paracetamol	2.836	5,090,858
Ibuprofen	10.190	2,021,018



Name	Retention time	Area
Paracetamol	2.844	4,785,478
Ibuprofen	10.398	10,101,248

Fig. 11: Dissolution sample of formulation F1

Disintegration test for paracetamol IR Layer

Model chromatograms

In vitro dissolution studies

Model chromatograms

Dissolution

Kinetic study for Paracetamol IR layer of bi-layer tablet

The data obtained for *in vitro* release were fitted into equations for zero-order, first-order, Higuchi, and Korsmeyer–Peppas release models. The interpretation of data was based on the value of the resulting regression coefficients.

From these values, it was observed that the first-order model was found to be best suited with R^2 value of 0.933.

Kinetic study for Ibuprofen SR layer of bilayer tablet

The data obtained for *in vitro* release were fitted into equations for zero-order, first-order, Higuchi, and Korsmeyer–Peppas release models. The interpretation of data was based on the value of the resulting regression coefficients.

From these values, it was observed that the Higuchi model was found to be best suited with R^2 value of 0.994.

DISCUSSION

Paracetamol is also known as acetaminophen, centrally acting analgesic derivative of p-aminophenol. Commonly used for its antipyretic and analgesic effects, which has a biological half-life of 1–4 h. Ibuprofen is described as 2-(4-isobutylphenyl)propionic acid and is a nonsteroidal compound, which exhibits high levels of anti-inflammatory, analgesic, and antipyretic activities necessary for the effective treatment of rheumatoid arthritis and osteoarthritis. The biological half-life of Ibuprofen is 2–4 h. This drug works by blocking the enzyme in your body that makes prostaglandins. Decreasing prostaglandins help to reduce pain, swelling, and fever. In the present work, an attempt was made to prepare bi-layer tablets of Paracetamol (IR) and Ibuprofen (SR) with excipients such as MCC, starch, PVP K-30, sodium starch glycolate, hydroxyl propyl methylcellulose E50LV, ethylcellulose, magnesium stearate, talc, and isopropyl alcohol. Prepared bilayered tablets were evaluated for hardness, friability, weight variation, drug content uniformity, drug-excipient interaction, and *in vitro* drug release, and stability studies. Among the various formulations prepared, Formulation F1 with SSG for Paracetamol release and HPMC E50LV for Ibuprofen release showed comparatively good release, which complies with the dissolution requirements.

CONCLUSION

In the present work, an attempt was made to design a combination of bi-layer tablets containing Paracetamol immediate-release layer and Ibuprofen sustained release layer. FT-IR studies reveal that there were no significant interactions between both the drugs and between the drugs and their respective excipients. For achieving immediately release of Paracetamol, polymer-like Sodium starch glycolate was used. For sustained release of Ibuprofen, polymers like HPMC E50LV were used. Here, F1 was

best formulation among them. Paracetamol release 97.87% after 40 min. Formulation F1 gave 97.65% drug release after 12 h. Therefore, F1 was selected as best formulation among F1–F5. The bi-layer tablets prepared formulated F1 shown good post-compression parameters such as hardness, and friability weight variation drug content which were within the limits. Both the drugs in bi-layer tablets are shown dissolution profiles within the limit. Since, HPMC E50LV is a good sustained release polymer. The combination of HPMC E50LV and CMC gave good sustained drug release for 12 h. From this study by preparing bilayer tablets, it was concluded that we could reduce the dosage frequency, dose-related side effects, and improve the bioavailability of drugs which in turn improves patient compliance. Thus, a fixed-dose combination tablet of Paracetamol and Ibuprofen were designed as bi-layer tablets which will have good patient compliance.

ACKNOWLEDGMENT

The author would like to thanks Dr. Dinesh Kaushik for providing a platform and facility to conduct research work. The authors would like to thanks Combotic Global Pvt. Ltd. for providing a gift sample of Ibuprofen and Paracetamol.

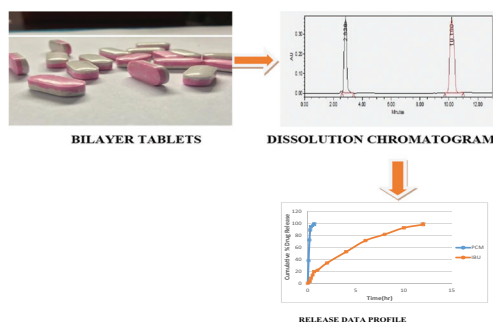
AUTHORS' CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

STRUCTURAL ABSTRACT



REFERENCES

1. Khaleel S, Patil P, Bhagat M. Bilayer tablet an emerging trend. *Eur J Pharm Med Res* 2017;4:471-80.
2. Gopinath C, Hima V. An overview on bilayered tablet technology. *J Glob Trends Pharm Sci* 2013;4:1085-98.
3. Verma R, Kishor D. Bi-layer tablets for various drugs. *Sch Acad J Pharm* 2014;3:271-9.
4. Bhatia E, Vaishy P, Mishra A, Pathak A. Bilayered tablet technology. *Int J Pharm Biol Arch* 2014;5:9-18.
5. Devtalu S, Patil A, Bari M. A review on novel approach bilayer tablet technology. *Int J Pharm Sci Rev Res* 2013;21:46-52.
6. Reddy P, Rao D, Kumar R. Bi-layer technology an emerging trend: A review. *Int J Res Dev Pharm Life Sci* 2013;2:404-11.
7. Trpathi KD. *Essentials of Medical Pharmacology*. 6th ed. New Delhi: Jaypee Brothers; 2003. p. 193, 198-9.
8. Shirse P. Formulation and evaluation of bilayer tablets of diclofenac sodium with ranitidine HCL for sustained and immediate release. *J Appl Pharm Sci* 2012;2:136-41.
9. Payghan S, Disuza J. Formulation, evaluation and development of bilayer tablet. *Int J Pharm Res Dev* 2011;3:80-7.
10. Darekar A, Jadhav S, Saudager R. Bilayer tablet technology: An overview. *Int J ChemTech Res* 2017;10:595-603.
11. Zhu C, Xu S, Han X, Wang W, He W, Yin L, *et al*. Sustained release bilayer tablet of ibuprofen and phenylephrine hydrochloride: Preparation and pharmacokinetics in beagle dogs. *AAPS PharmSciTech* 2019;20:86.
12. Sarangi MK, Chowdary K, Sundriyal A. Formulation development and evaluation of bilayer tablets containing paracetamol sr and tizanidine. *J Appl Pharm* 2014;6:347-59.
13. Sudhakar M, Rao V, Samalla N. Development and optimization of paracetamol immediate release and aceclofenac controlled release bilayer tablets. *Am J Adv Drug Deliv* 2013;1:93-101.
14. Yasmeen Z, Mamatha T, Farheen H. Dissolution method development and validation for combination of ibuprofen and paracetamol tablets. *Asian J Pharm Clin Res* 2013;6:162-6.
15. Payghan S, Disuza J. Formulation, evaluation and development of bilayer tablet. *Int J Pharm Res Dev* 2011;3:80-7.
16. Islam SA, Banu H, Mostafa R. Bilayer tablets of paracetamol and aceclofenac: formulation and evaluation. *Int J Pharm Technol* 2011;17:811-22.
17. Hosna B, Sahariar M, Shahdaat M. Formulation development of bilayer acetaminophen tablets for extended drug release. *J Chem Pharm Res* 2011;3:348-60.
18. Biljana G, Rade I. Formulation and evaluation of immediate release tablets with different types of paracetamol powders prepared by direct compression. *Afr J Pharm Pharmacol* 2011;5:31-41.
19. Rahman M, Roy S. Evaluation of various grades of hydroxypropylmethylcellulose matrix systems as oral sustained release drug delivery systems. *J Pharm Sci Res* 2011;3:930-8.
20. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bilayer tablet of metoclopramide hydrochloride and ibuprofen. *AAPS PharmSciTech* 2008;9:818-27.
21. Indian Pharmacopoeia. Government of India, Ministry of health and family welfare. Ghaziabad: Published by The Indian Pharmacopoeia Commission; 2018. p. 1217-8, 1514-7.
22. Saiesh P, Shabaraya AR, Shripathy D. Kinetic modelling of drug release. *Int J Univ Pharm Biosci* 2014;3:92-104.