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Development and characterization of bilayer tablets of Paracetamol and Diclofenac sodium

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ABSTRACT: Background: The paracetamol and diclofenac sodium are NSAIDs class of drugs extensively used for antipyretic and analgesic activities**. Aim:** Present research work aimed to develop a bilayer tablet of paracetamol and diclofenac sodium. **Methods**: The bilayered tablet of paracetamol and diclofenac sodium was manufactured using polymers, cross povidone and sodium starch glycollate in fast dissolving first layer and hydroxyl propyl methyl cellulose (HPMC) in control release second layer by wet granulation method at various concentrations. The prepared granules and compressed tablets were evaluated for flow properties, tablet diameter, thickness, weight variation, hardness, friability, disintegration, content uniformity and dissolution test. **Results:** The flow property of granules was good. The value of all physiocchemical properties of tablets were satisfactory and were within the Pharmacopeia limit. The drug content was maximum (93.2 and 94.4 %) for the tablet formulation F6 (A6) and F3 (B3). The *in vitro* drug release profile showed considerable drug release profile for all the tablet batches. **Conclusion:** Among all the tablet formulations, the modified tablet formulations in the form of F6 (A6) and F3 (B3) showed excellent drug content and release profile (93.4 and 92.6 % in 30 min and 10 h) with more sustained manner. Thus this formulation of Paracetamol and diclofenac sodium bilayer tablets were found promising and as potential alternative to the conventional dosage form of the drugs.

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INTRODUCTIONS:

Among all the routes of administration, the oral ingestion is the predominant and most preferable route, through which more than 50 % of drug deliveries available in the market. From many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectable, as a drug carriers [1]. Even today

these conventional drug delivery systems are the primary pharmaceutical products commonly seen in the prescriptions as it provide a prompt release of drug. Therefore to achieved and maintain the drug concentration within the therapeutically range need for treatment; it is often to take this type of delivery system several times a day. This results in a significant fluctuation in the drug delivery [1-3]. Novel drug delivery systems (NDDS) offer a promising approach for controlled and site specific delivery to the gastro-intestinal (GI) track by attaching the devices to the site of action. The controlled release systems are also known to provide intimate contact between the dosage form and the absorptive mucosa, resulting in high drug flux through the absorbing tissue with improved bioavailability. These delivery systems were proven to be suitable for the purpose of reduction of transit time of the dosage form through the GI track [4]. Tablets with different proportions of polymer, drug will be prepared by direct compression technique. Tablets may be of different forms for controlled release; likely Matrix tablets, Bi-layer tablets and Floating tablets. The multilayered tablet concept has been long utilized to develop sustained release formulations. Such a tablet has a fast releasing layer and may contain bi- or triple layers to sustain the drug release. The pharmacokinetic advantage relies on the fact that drug release from fast releasing granules leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining granules [5,6]. The paracetamol is a widely used over-the-counter opoid analgesic and antipyretic. In combination with opioid analgesics, paracetamol can also be used in the management of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients. The onset of analgesia is approximately 11 min after oral administration of paracetamol and its half-life is 1 to 4 h. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic. Its protein binding is 99 %, $t_{1/2}$ is 1 to 2 h. So, the objective of the proposed work is to develop a Novel Drug Delivery System (NDDS) in the form of tablet containing a controlled release component forming the suitable dosage form [7,8].

MATERIALS AND METHODS:

Paracetamol and Diclofenac sodium were procured as gift sample from Alkem Laboratories Ltd, India. Sodium starch glycollate, Crospovidone and HPMC were procured from Himedia Ltd., India. All other chemicals and reagents were of analytical grade and were procured from authorized dealers.

Formulation of the fast release layer:

The first layer of tablet that is fast release granules were prepared by wet granulation technique by blending the drug (Paracetamol) uniformly with sodium starch glycollate, crospovidone and microcrystalline cellulose at different batches using starch paste (15 % w/v) as binder as per the given formulae. The cohesive mass obtained was passed through a 1000 µm sieve and it was dried at 60 °C for 1 h. The granules were again passed through a 1000 µm sieve to break up agglomerates. The granules were then mixed with talc and magnesium stearate (Table 1) [9].

Table 1. Formulation composition of the fast release layer (Part-A) of tablet.

Sl. no.	Ing. (mg)	Formulations					
		F1	F2	F3	F4	F5	F6
1	PCM	500	500	500	500	500	500
2	CPD	5	10	15		-	-
3	SSG	-	-	-	50	40	30
4	Starch	40	40	40	40	40	40
5	MCC	53	47	42	8	18	28
6	MP	0.37	0.37	0.37	0.37	0.37	0.37
7	PP	0.07	0.07	0.07	0.07	0.07	0.07
8	MS	1	1	1	1	1	1
9	Talc	1	1	1	1	1	1

PCM – Paracetamol, CPD – Cross providone, SSG – Sodium starch glycollate, MCC – Microcrystalline cellulose, MP – Methyl Paraben, PP – Propyl Paraben and MS – Magnesium stearate.

Formulation of the sustained release layer:

The granules for sustaining layer of the tablets were also formulated by the wet granulation technique by mixing the drug individually with HPMC uniformly. Then lactose was added as diluent. Starch paste (15 % w/v) was incorporated as binder. The sustaining granules were also subjected to similar processing steps as the fast releasing granules (Table 2) [9].

Compression of bilayer tablets:

The granules for the sustained release layer was compressed lightly using a single punch-tableting machine (Rimek Mini Press 1, Shakti Engineering Ltd, India) equipped with 35 station rotatory punching

machine (Accura Press 11) equipped with 12 mm round, flat and plain punches.

Table 2. Formulation composition of the sustained release layer (Part-B) of tablet.

Sl no.	Ing. (mg)	Formulations					
		F1	F2	F3	F4	F5	F6
1	DFS	100	100	100	100	100	100
2	HPMC	100	90	80	70	60	50
3	Lact.	17.5	27.5	37.5	47.5	57.5	67.5
4	MP	0.37	0.4	0.37	0.37	0.37	0.37
5	PP	0.07	0.07	0.07	0.07	0.07	0.07
6	CYL	1.00	1.0	1.00	1.00	1.00	1.00
7	MS	0.50	0.5	0.50	0.50	0.50	0.50
8	Talc	1	1	1	1	1	1

DFS – Diclofenac sodium, CPD – Cross providone, MP – Methyl Paraben, PP – Propyl Paraben, CYL – Color Sun Yellow Lake and MS – Magnesium stearate.

Table 3. Pre-compression data of various granules.

FC	AOR (°) (X±S.D.)	Carr's Index (X±S.D.)	Hausner Ratio
A1	25.3±0.363	14.01±0.509	1.206
A2	24.2±0.259	13.01±0.331	1.115
A3	22.1±0.244	11.34±0.162	1.1013
A4	26.7±0.735	17.31±0.649	1.1724
A5	24.5±0.338	14.05±0.947	1.1604
A6	21.4±0.567	14.35±0.845	1.1912
B1	22.3±0.363	14.21±0.509	1.2086
B2	24.2±0.259	12.03±0.361	1.1142
B3	23.1±0.244	13.34±0.162	1.1134
B4	25.7±0.735	17.31±0.659	1.1734
B5	24.5±0.338	15.05±0.977	1.1656
B6	22.4±0.567	13.35±0.856	1.1965

All data are represented as mean ± standard deviation (n = 3). Standard Error of Mean < 0.564. FC – Formulation code and AOR – Angle of repose.

Over this compressed layer, the required quantity of granules for the fast release layer were placed and compressed again to obtain the hardness of the resultant tablets in the range of 3-5 kg/cm^2 [10,11].

Pre-compression evaluation studies [12,13]:

Flow Properties:

The powder blend was evaluated for flow properties such as bulk density, tapped density, compressibility index and Hausner ratio to assure weight and dose accuracy during compression for commercial aspect. The angle of repose was determined by fixed funnel method. The blend were tapped using bulk density apparatus (Excel Enterprises, Kolkata) for 1000 taps in a cylinder and the change in volume were measured. Carr index and Hausner ratio were calculated by the formula:

Carr index (%) = $(D_f\text{-}D_0) \times 100 / D_f$ ..... (1)

Hausner ratio = D_f / D_0 ..... (2)

Where, D_f is poured density; D_0 is tapped density. All the experimental units were studied in triplicate (n=3).

Table 4. Evaluation data of bilayered tablet formulations.

FC	TV (cm) (X±S.D.)	WV (mg) (X±S.D.)	HD (Kg/cm^2) (X±S.D.)
A1	0.41±0.03	599 ±3.8	5.5±0.8
A2	0.40±0.02	601±2.92	6.1±0.5
A3	0.39±0.02	598±4.4	6.0±0.3
A4	0.41±0.06	599±2.21	6.3±.0.7
A5	0.39±0.04	600±3.78	5.4±0.8
A6	0.40±0.05	598±4.89	5.2±0.4
B1	0.42±0.04	219 ±3.6	5.6±0.8
B2	0.41±0.05	221±2.94	6.3±0.5
B3	0.42±0.03	219±3.4	6.2±0.3
B4	0.39±0.05	221±3.21	6.0±.0.7
B5	0.42±0.02	219±4.78	5.2±0.8
B6	0.40±0.04	220±4.79	5.1±0.4

All data are represented as mean ± standard deviation (n = 3). Standard Error of Mean < 2.821. FC – Formulation code, TV – Thickness variation, WV – Weight variation and HD – Hardness.

Evaluation of bilayer tablets:

Tablet thickness and diameter:

The thickness of a tablet is only dimensional variable related to the compression process. The tablet thickness should be controlled within ± 5 % variation of standard value. The thickness of tablets was measured out using Digital Venire calipers (Mitutoyo, Chaina) [14,15].

Tablet hardness:

The capacity of the tablets to withstand the stress during shipping or shifting, during storage, during

transportation and during handling before utilized by the consumer depends on its hardness. The hardness of the prepared tablets was determined by using Monsanto Hardness Tester (Ketan Eng. Ltd, Mumbai) [14,15].

Table 5. Friability, DT and drug content of various bilayered tablet formulations.

FC	DT (s)	DC (%)	Friability (%)
A1	4:25	77.01	0.921
A2	4:35	74.4	0.882
A3	4:16	72.21	0.781
A4	4:28	69.08	0.912
A5	4:56	86.12	0.814
A6	4:55	93.20	0.712
B1	6:78	70.04	0.543
B2	6:47	89.12	0.784
B3	6:48	92.16	0.872
B4	6:57	93.16	0.642
B5	6:72	93.07	0.784
B6	6:84	94.4	0.746

FC – Formulation code, DT – Disintegration time and DC – Drug content.

Friability Test:

Friability is another measure of tablet strength. Roche Friabilator (Friabilator USP EF-2, Electrolab, Mumbai) was used for testing the fragmentation phenomenon of the tablets. Twenty tablets in a row were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 100 rotations, the tablets were weighed and the percentage loss in tablet weight was determined [14,15].

Weight variation test:

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance (Essae - Teraoka Ltd,U.K.). The average weight of one tablet was determined from the collective weight [16,17].

Drug content uniformity for Paracetamol:

About 20 tablets were weighed and powdered. A quantity of the powder containing equivalent 500 mg of paracetamol was taken and extract with 20 ml of acetone and it was filtered. The filtrate was dried. The 1 ml of strong HCl was add to 0.1 g of residue and it was heated to boiling and boiled for 3 min and then cooled. From this solution, 10 ml was taken and then 0.05 ml of 0.0167 M potassium dichromate was added. A violet color was developed. The paracetamol content in solution was analyzed using UV-Visible spectrophotometer (UV 1800, Shimadzu, Japan) at λ_{max} of 244 nm [18,19].

Drug content uniformity for Diclofenac sodium:

About 20 tablets were weighed and powdered. A quantity of the powder containing equivalent 50 mg of diclofenac sodium was taken and it was shaken with 60 ml of methanol in a 200 ml volumetric flask and diluted to volume with methanol. The 5.0 ml of this solution was diluted to 100.0 ml with methanol and the absorbance was measured at λ_{max} of about 256 nm against blank [18,19].

Disintegration time:

Disintegration test was carried out in USP type disintegration apparatus (Electrolab, Kolkata) using 900 of simulated gastric fluid that is 0.1 N HCl of pH 1.2 at 37±2 °C [20,21].

In-vitro drug dissolution study:

Dissolution study was carried out in USP XXXI type II dissolution apparatus (paddle type) in (TDT 08L, Electrolab, Kolkata). Dissolution study was performed at 50 rpm in 900 ml of simulated gastric fluid (0.1 N HCl) of pH 1.2 for the first 2 h and followed by simulated intestinal fluid of pH 6.8 phosphate buffer for the remaining h. The temperature was maintained at 37 ± 0.2 °C. An aliquot of 5 ml sample was withdrawn at a predetermined time interval of 5, 10, 15, 20, 25, 30, 60, 120, 180, 240, 300, 360, 420, 480, 540 and 600 min. Then the sample was filtered through Whatmann filter paper No 24. The absorbance of withdrawn sample was measured by UV-Visible spectrophotometer at λ_{max} of 244 nm for paracetamol and 256 nm for diclofenac sodium [22,23].

Statistical analysis:

All the results obtained during evaluation, were verified with different statistical methods like mean, standard deviation, standard error mean[24].

RESULTS AND DISCUSSIONS:

The bulk densities for the granules of various formulations ranged between 0.502±0.675 to 0.582±0.758 g/ml, as determined by the tap density method. This value of bulk density indicates of good packing character. The compressibility index (carr's index) for all the formulations was found to be almost below 17 % (Table 3), indicated desirable good flow

properties. Hausner ratio also calculated for the granules flow property determination and seems to be within the range i.e.; below 2.5. The angle of repose for all granules; it ranged between 21.39±0.567 to 26.75±0.735 ° (Table 3)**.** The value indicates good flow properties of granules. All the batches of both the layers of bilayer tablets were produced under similar conditions to avoid processing variables. Physicochemical properties of the tablets were evaluated, where the weight variation, thickness and diameter values of each of the formulations were found to be within the I.P. limits.

Table 6. *In vitro* drug release data of fast releasing layer of all tablet formulations.

Time (min)	Percentage Cumulative Release					
	A1	A2	A3	A4	A5	A6
5	21.5	21.82	20.82	18.36	24.37	26.83
10	30.9	30.70	29.70	28.36	33.93	36.25
15	41.2	40.10	38.50	37.86	42.75	48.39
20	52.7	50.19	49.11	47.65	54.99	62.89
25	64.1	63.40	59.06	58.23	68.35	78.48
30	77.0	74.41	72.61	69.86	86.49	93.44

Table 7. *In vitro* drug release data of sustained releasing layer of all tablet formulations.

Time (h)	Percentage Cumulative Release					
	F1	F2	F3	F4	F5	F6
1	3.3	4.4	3.9	3.6	16.3	14.7
2	7.1	7.8	8.8	22.8	29.5	26.9
3	12.5	14.6	15.9	32.3	42.8	37.7
4	22.6	25.8	27.5	44.3	56.6	51.3
5	32.5	34.4	38.6	56.5	62.5	63.3
6	43.6	45.7	46.5	68.7	78.5	72.3
7	50.2	54.7	58.9	84.8	93.7	84.6
8	58.4	62.5	67.6	94.7	-	92.9
9	64.2	74.4	79.9	-	-	-
10	70.5	80.4	92.6	-	-	-

Average weight of different layers of bilayer tablets was found to be 600±2 mg for fast release layer (A) and 220±2 mg for sustained release layer (B) (Table 4). The hardness was found to be in the ranges of 5.1 to 6.3 kg/cm^2 (Table 4), where as thickness was 0.40±0.02 cm on an average for all the tablet formulations (Table 4). The percentage friability of all the formulations was found to be less than 1 % (Table 5), as per USP specification. Thus all tablet formulations passed for friability test. Values of hardness test and percent friability indicates good handling properties of both the layer of bilayer tablet. All the batches of both the layers of bilayer tablets were evaluated for disintegration test under similar conditions to avoid processing variables. The disintegration time for all formulations was found to be less than 7 s (Table 5). Drug content from the prepared formulations ware studied. The drug content in fast release layer was found in the range 72.12 to 93.2 % and drug content for sustained release layer was found in range 70.04 to 94.4 % (Table 5). Almost all tablet formulations exhibited satisfactory drug content. The drug percentage released data conclude that the bilayered tablet formulation, A6 from fast releasing layer and formulation B3 form sustained releasing layer, released maximum amount of drug in sustained manner. gave maximum % drug release in formulation of sustained releasing layer (Part B) formulation B4, B5 and B6 also give higher releasing values but they gave their maximum release in 8,7 and 8 h respectively therefore these are not act as in sustained manner. So on basis of above discussion formulation A6 for fast releasing layer and B3 for sustained releasing layer are slect as best optimized formulations.

CONCLUSION:

The present investigation showed that as we go on increasing the concentration of polymers in the formulations it leads to increase in the release rate of the tablet. The drug percentage released data conclude that the bilayered tablet formulation, A6 from fast releasing layer and formulation B3 form sustained releasing layer, released maximum amount of drug in sustained manner. Extensive physicochemical evaluations and *in vitro* drug release study concluded that the dissolution profile of the entire tablet formulations entirely depend on the type, composition and concentration of polymers incorporated in it. Further more intensive studies regarding *in-vivo* drug release and *in vitro in vivo*, correlation of the pharmacokinetic parameters is highly demanding to develop this formulation to serve the mankind for maximum therapeutic benefit.

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