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FORMULATION AND EVALUATION OF BILAYER TABLETS OF ANTI-INFLAMMATORY DRUGS

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ABSTRACT

Bilayer tablet is the new time for the effective advancement of controlled discharge detailing. It is additionally called Double or Multi part tablet. Bilayer tablet is superior to the generally utilized measurements structure. It likewise fit for isolating two kinds of contradictory substances and furthermore for support discharge tablet in which one layer is quick delivery as beginning portion and second one is sustained portion. In the present study of bilayer tablet preparation paracetamol immediate release layer and another layer aspirin is sustained release were prepared by the direct compression method. For primary trials F1 to F10 prepared layer was evaluated for weight variation, thickness, hardness, friability, DT, WT, drug content, drug release, among the total 10 batches F2 has been satisfied above all criteria. Pre-formulation study was carried for the drug and excipients and it has shown that drug and all the excipients have better flow property and compressibility.

KEYWORDS

Bilayer tablet, Pre-formulation study, Paracetamol, Immediate release, Aspirin, Sustained release and Direct compression method.

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INTRODUCTION

The oral medication conveyance market is the biggest fragment of the medication conveyance market and there's no sign that it is dialing back. Oral course of medication organization have wide acknowledgment up to 55-65% of all out dose structure and is the most helpful and favored course for fundamental impact because of its simplicity of dosing organization, torment evasion, exact measurement, patient consistence and adaptability in plan. The significant point of controlled drug

conveyance is to decrease dosing recurrence. The plan of changed discharge drug item are to upgrade a helpful routine by giving sluggish and constant conveyance of medication over the whole dosing stretch and give better persistent consistence and patient comfort. More than 70% of the definitions produced today are ingested orally[1,2].

Paracetamol (N-acetyl-p-aminophenol) is a non-opioid analgesic and antipyretic agent used to treat fever and mild to moderate pain. It's relieves pain in both acute mild migraine and episodic tension headache. The aspirin/paracetamol/caffeine combination also helps with both conditions where the pain is mild and is recommended as a first-line treatment for them[3,4]. Aspirin (Acetyl salicylic acid) is one of non-steroidal anti-inflammatory drugs (NSAIDs). It's widely used to relieve mild to moderate pain and inflammation. It's works as an antiplatelet agent by irreversibly blocking the enzyme cyclooxygenase-1 (COX-1) inside the platelets. This enzyme is necessary to generate thromboxane A2, a potent platelet activator from arachidonic acid[5,6].

Purpose of this study, from through literature search there are few bilayer and multiple layer formulation available in paracetamol with other drug combination and aspirin other drug combination. The very few bilayered formulation available in paracetamol with combination aspirin but there are initial stage and not satisfied[7,8].

Ideal Characteristics of Bilayer Tablet[9,10]

It ought to have adequate solidarity to endure mechanical shock during its creation, bundling, transporting and apportioning.

It ought to have smooth item character, liberated from absconds like chips, breaks, staining and defilement.

Should have a substance dependability timeframe of realistic usability, so as not to follow change of the restorative specialists.

The bilayer tablet should deliver drug in an expectable and reproducible way.

It ought to have physical and compound soundness to keep up with its actual characteristics after some time.

Challenges in Bilayer Tablet Manufacturing[11,12]

Theoretically, bilayer tablets should be visible as two single-layer tablets compacted into one. By and by, there are some assembling difficulties.

Delamination

Tablet self-destructs when the two parts of the tablet don't bond totally. The two granulations ought to stick when compacted.

Cross-tainting

At the point when the granulation of the main layer mixes with the granulation of the subsequent layer or the other way around, cross-defilement happens. It might overcome the reason for the bilayer tablet.

Creation yields

To forestall cross pollution, dust assortment is required which prompts misfortunes. In this manner, bilayer tablets have lower yields than single-layer Tablets.

MATERIAL AND METHODS

List of chemicals and list of equipments used has been given in the Table No.1 and Table No.2 respectively.

Experiment

Pre-formulation Study

Pre-formulation studies are the first step in the rational development of dosage form of a drug substance. The objective of pre-formulation studies is to develop a portfolio of information about the drug substance, so that this information useful to develop different dosage form. Pre-formulation can be defined as investigation of physical and chemical properties of drug substances alone and when combined with excipients. A Pre-formulation study was carried out with potential formulation excipients to determine drug-excipients interaction/ compatibility. The flow properties of drugs and excipients are evaluated like bulk density, tapped density, compressibility index, hausner's ratio, angle of repose.

Formulation Development

Preliminary screening of super-disintegrating agent for immediate release layer of Paracetamol

The development of the immediate release layer containing Paracetamol by selecting ingredients in the appropriate amount and the super-disintegrants optimized thereafter. The immediate release layer of Paracetamol was prepared by the direct compression method. Sodium starch glycolate, croscarmellose sodium were used in varying amounts as shown in table 1. Batch F1 to F3 contained 2%, 3%, and 5% of sodium starch glycolate, respectively. Batch F4 to F6 contained 2%, 3%, and 4% croscarmellose sodium, respectively and batch F6 to F10 contained 2%, 3%, 4%, and 5% ac-di-sol® respectively (Table No.3). Prepared layer was evaluated for weight variation, thickness, hardness, friability, disintegration time, wetting time, drug content, and % cumulative drug release at 15 min.

Sustained Release Layer of Aspirin

(Preliminary screening of polymer for sustained release layer of Aspirin)

The development of a sustained release layer containing aspirin 300mg by selecting ingredients in the appropriate amount and polymer were optimized thereafter. The sustained release layer of Aspirin was prepared by the direct compression method. HPMC K4M, HPMC K100M, Polyoxtm WSR 301 and Polyoxtm WSR 303 were used in various amounts as shown in table 4.0. Batch F1 was prepared with HPMC K4M and Polyoxtm WSR 301. Batch F2 prepared to check the effect of HPMC K4M with Polyoxtm WSR 301. Batch F3 and F4 was prepared with HPMC K15M with different grade of Polyoxtm WSR. Batch F5 and F10 was developed to check the effect of HPMC K100M different grade of Polyoxtm WSR (Table No.4). Prepared layer was evaluated for weight variation, thickness, hardness, friability, disintegration time, drug content, and % cumulative drug release.

RESULTS AND DISCUSSION

Physical Compatibility

After 1 month all samples were visually observed. Both drugs were found to be compatible with all the excipients used in formulation. The visual inspection of stored powder mixtures of paracetamol and aspirin with different proportion of excipients did not show any change in colour or appearance (e.g. discoloration, caking, liquefaction, formation of clumps). This represents a good preliminary indication of physical stability. The API-excipients physical mixtures were analyzed visually, the results are showed in Table No.5 and Table No.6.

PHYSICAL CHARACTERIZATION OF PARACETAMOL AND ASPIRIN

Flow Properties of Drug and Excipients

From the above table 5.0 and 6.0, it was concluded that Paracetamol, Aspirin, Sodium Starch Glycolate, Acdisol, Crospovidone, MCC PH102, Tablattose, HPMCK100, PolyoxWSR303, Ethyl cellulose, Magnesium Stearate have excellent flow property based on angle of repose because they all have angle of repose value between 19.52 ± 2.41 to 28.22 ± 2.73. They all have Carr's index value between 9.6 ± 0.2 to 15.0 ± 0.2% and Hauser's ratio 1.10 ± 0.3 to 1.23 ± 0.3 between showed excellent to good compressibility (Table No.7). Post-Compression Evaluation Parameters of Preliminary Batches has been given in the Table No.8.

***In-vitro* Drug Release Study for Paracetamol and Aspirin**

In-vitro release of bilayer tablets was determined using a USP type -II dissolution test apparatus at 100rpm. The dissolution was studied using 900ml of simulated gastric fluid 0.1N HCl (without enzyme, pH 1.2) for the first 2 hr and followed by a simulated intestinal fluid (without enzyme, pH 6.8) for the remaining 10 hr. The temperature was maintained at 37 ± 0.5^0C. 5ml sample was taken and replaced at different time intervals up to 12 hr and the parameters of dissolution were given in Table No.9. Filter through whatman filter paper and replaced by an equal volume of dissolution medium

sample were suitably diluted and analyzed by HPLC at 243 and 273nm paracetamol and aspirin respectively. *In-vitro* Drug Release of paracetamol Batches F1 to F10 given in the Table No.10 and *In-vitro* Drug Release of aspirin Batches F1 to F10 given in the Table No.11.

Preliminary batches F1 to F6 were prepared using different polymers like HPMC K4M, HPMC K15M, HPMC K100M, Polyox^{tm} WSR301, Polyox^{tm} WSR 303. Batches were prepared using different concentration of each polymer and have shown drug release before 10 hrs in HPMC K100M, Polyox^{tm} WSR 303 containing formulations as compare to other polymer. To achieve drug release up to 10hrs, it was necessary to combine the concentration of polymer in the formulations. Among these polymers, batches having HPMC K100M and Polyox^{tm} WSR303 have indicated better sustained drug release compared to batches having other polymers.

Table No.1: List of materials and equipments used

S.No	Materials	Suppliers
1	Paracetamol	Par Formulation, Chennai.
2	Aspirin	Par Formulation, Chennai.
3	MCC PH102	S.D. Fine Chemicals
4	HPMC K4M	S.D. Fine Chemicals
5	HPMC K15M	S.D. Fine Chemicals
6	HPMC K100M	S.D. Fine Chemicals
7	Polyox^{tm}WSR301	S.D. Fine Chemicals
8	Polyox^{tm} WSR303	S.D. Fine Chemicals
9	Ethyl cellulose	Colorcon Asia Pvt Ltd.
10	Quinoline yellow	S.D. Fine Chemicals
11	Tablattose	ACS Chemicals Ltd.
12	Sodium Starch Glycolate	ACS Chemicals Ltd.
13	Cros povidone	ACS Chemicals Ltd.
14	Magnesium Stearate	S.D. Fine Chemicals

Table No.2: Equipments used in present investigation

S.No	Instruments	Manufacturer
1	Digital weighing balance	Shimadzu AUX 220 (Uni Bloc)
2	Hot air oven	Janki Impex Pvt. Ltd.
3	Friabilator (USP)	Electrolab EF2
4	USP dissolution tester	Electrolab TDT-06 P Dissolution Tester)
5	Rotary Tablet Punching Machine	Karnavati Engineering, Ahmedabad
6	Hardness Tester	Monsanto hardness tester
7	Vernier Caliper Scale	Mitutoyo, Japan
8	Sonicator	Janki Impex Pvt. Ltd.
9	Orbital Flask Shaker	Deqing fengda electric, Co. Ltd. FD1238A
10	FTIR	Shimadzu 8400S, Japan
11	DSC	Shimadzu DT-60

Table No.3: Preliminary screening of super disintegrating agent for immediate release of Paracetamol

S.No	Ingredients (mg)	Qty. (mg/tab)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Paracetamol	500	500	500	500	500	500	500	500	500	500
2	Microcrystalline Cellulose	51	50	48	51	50	49	51	50	49	48
3	Tablattose	20	20	20	20	20	20	20	20	20	20
4	Sodium starch glycolate	2	3	5	0	0	0	0	0	0	0
5	Croscamellose sodium	0	0	0	2	3	4	2.5	3.5	4.5	5
6	Magnesium stearate	1	1	1	1	1	1	1	1	1	1
7	Talc	1	1	1	1	1	1	1	1	1	1
8	Total	575mg/tab									

Table No.4: Preliminary screening of super disintegrating agent for Sustained release of Aspirin

S.No	Ingredients (mg)	Qty. (mg/tab)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Aspirin	300	300	300	300	300	300	300	300	300	300
2	MCCPH102	88.8	88.8	88.8	88.8	88.8	88.8	88.8	88.8	88.8	88.8
3	HPMC K4M	30	30	-	-	-	-	30	30	95	95
4	HPMC K15M	-	-	30	30	-	-	-	-		
5	HPMC K100M	-	-	-	-	30	30	-	-	35	25
6	Polyox^{tm} WSR301	30	-	30	-	30	-	30	-	25	35
7	Polyox^{tm} WSR303	-	30	-	30	-	30	-	30		
8	Quinoline yellow	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
9	Magnesium stearate	1	1	1	1	1	1	1	1	1	1
10	Total	450mg/tab									

Table No.5: Observation of Paracetamol-excipients compatibility

S.No	Drug + Excipients	Ratio	Initial	After 1 month at Room Temperature in Desigator
1	Paracetamol	1	A white or almost white crystalline powder	No Change
2	Paracetamol + MCC	1:1		No Change
3	PH102			
4	Paracetamol +	1:1		No Change
5	Tablattose			
6	Paracetamol + SSG	1:1		No Change
7	Paracetamol + Acdisol	1:1		No Change
8	Paracetamol +	1:1		No Change
9	CrosPovidone			
10	Paracetamol +	1:1		No Change
11	Magnesium Stearate			

Table No.6: Observation of aspirin-excipients compatibility

S.No	Drug + Excipients	Ratio	Initial	After 1 month at Room Temperature in Desigator
1	Aspirin	1	A white or almost white crystalline powder	No Change
2	Aspirin +	1:1		No Change
3	MCC PH102			
4	Aspirin +	1:1		No Change
5	HPMCK100			
6	Aspirin +Polyox^{tm} wsr303	1:1		No Change
7	Aspirin +	1:1		No Change
8	Ethyl cellulose			
9	Aspirin +Magnesium Stearate	1:1		No Change

Table No.7: Flow properties of drug and excipients

S.No	Ingredients	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
1	Paracetamol	0.62 ± 0.003	0.72 ± 0.002	15.46 ± 0.4	1.14 ± 0.5	28.9 ± 0.64
2	Aspirin	0.64 ± 0.02	0.69 ± 0.4	14.38 ± 0.3	1.16 ± 0.1	27.35 ± 2.73
3	Sodium Starch Glycolate	0.66 ± 0.01	0.62 ± 0.3	15.28 ± 0.3	1.16 ± 0.2	27.67 ± 2.94
4	Acdisol	0.68 ± 0.03	0.60 ± 0.3	14.0 ± 0.2	1.17 ± 0.3	25.47 ± 2.75
5	Crospovidone	0.62 ± 0.02	0.66 ± 0.2	13.5 ± 0.3	1.14 ± 0.3	29.17 ± 2.65
6	Tablattose	0.65 ± 0.03	0.64 ± 0.3	11.8 ± 0 .2	1.10 ± 0.3	27.81 ± 2.83
7	HPMC K100	0.69 ± 0.02	0.64 ± 0.3	13.7 ± 0.3	1.12 ± 0.2	26.22 ± 2.73
8	Ethyl Cellulose	0.67 ± 0.05	0.71 ± 0.03	11.3 ± 0.2	1.23 ± 0.3	25.71 ± 2.25
9	Polyox^{tm}wsr303	0.68 ± 0.01	0.70 ± 0.05	14.2 ± 0.3	1.20 ± 0.2	22.66 ± 2.65
10	MCC PH102	0.63 ± 0.04	0.74 ± 0.03	13.4 ± 0.3	1.18 ± 0.3	21.45 ± 2.41
11	Magnesium stearate	0.68 ± 0.02	0.75 ± 0.03	13.5 ± 0.2	1.21 ± 0.4	23.59 ± 2.31

All values are expressed as mean ± standard deviation, n=3

Table No.8: Post-compression evaluation parameters of preliminary batches

Batch Code	Weight variation	Thickness(mm)	Hardness (kg/cm^2)	% Friability	% Drug Content
F1	Pass	4.76 ± 0.074	3.30 ± 0.08	0.40 ± 0.02	99.8 ± 0.14
F2	Pass	4.56 ± 0.037	3.22 ± 0.06	0.42 ± 0.05	99.7 ± 0.75
F3	Pass	4.58 ± 0.023	3.18 ± 0.03	0.48 ± 0.03	100.5 ± 0.37
F4	Pass	4.67 ± 0.033	3.26 ± 0.02	0.46 ± 0.05	98.7 ± 0.18
F5	Pass	4.86 ± 0.075	3.35 ± 0.04	0.42 ± 0.04	98.6 ± 0.43
F6	Pass	4.58 ± 0.041	3.28 ± 0.01	0.44 ± 0.07	99.4 ± 0.23
F7	Pass	4.78 ± 0.034	3.32 ± 0.03	0.52 ± 0.08	99.3 ± 0.23
F8	Pass	4.88± 0.039	3.39 ± 0.04	0.55 ± 0.05	98.8 ± 0.23
F9	Pass	4.58 ± 0.045	3.19 ± 0.01	0.49 ± 0.03	99.1 ± 0.23
F10	Pass	4.37 ± 0.057	3.62 ± 0.03	0.47 ± 0.04	98.4 ± 0.23

All values are expressed as mean ± standard deviation, n=6

Table No.9: Parametors of Dissolution Study

S.No	Condition	For Paracetamol IR Tablet	For Aspirin SR Tablet
1	USP Dissolution apparatus	Type II (Paddle)	Type II (Paddle)
2	Media	0.1 N HCl	Phosphate Buffer pH 6.8
3	Volume of diss. Medium	900ml	900ml
4	Speed of paddle rotation	100RPM	100RPM
5	Temperature	$37^0 \pm 0.5^0$C	$37^0 \pm 0.5^0$C
6	Sampling point	5,10,15,30,45,60 min	0.5,1,2,4,6,8, 10 hr

Table No.10: *In-vitro* Drug Release of Batches F1 to F10

S.No	Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	5	47.4 ± 1.81	50.2 ± 2.18	51.1 ± 2.37	44.2 ± 1.74	46.8 ± 1.51	48.3 ± 2.54	55.6 ± 1.91	58.3 ± 2.14	61.7 ± 2.36	62.1 ± 2.09
2	10	58.2 ± 2.78	60.1 ± 2.36	62.5 ± 1.84	50.5 ± 1.85	55.9 ± 2.80	59.7 ± 2.86	62.4 ± 2.78	68.6 ± 1.81	74.5 ± 2.48	74.2 ± 2.35
3	15	75.4 ± 2.81	77.9 ± 2.51	77.3 ± 1.25	70.5 ± 1.39	72.3 ±1.15	75.3 ± 2.87	81.4 ± 2.44	83.3 ± 2.34	86.9 ± 1.46	86.9 ± 1.12
4	20	85.3 ± 2.42	88.4 ± 2.18	89.7 ± 1.61	75.4 ± 2.15	79.6 ±1.89	84.6 ± 2.22	89.7 ± 2.28	90.1 ± 2.81	91.2 ± 2.93	91.4 ± 2.65
5	30	98.6 ± 1.87	98.9 ± 2.59	99.2 ± 1.56	88.4 ± 2.69	90.7 ± 1.98	92.8 ± 2.29	98.6 ± 2.08	99.7 ± 2.25	99.9 ± 1.47	98.8 ± 2.29

All values are expressed as mean ± standard deviation, where n=3

Table No.11: *In-vitro* Drug Release of Preliminary Batches F1 to F10

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	18.5± 0.98	19.7± 0.57	19.9± 0.45	17.3±0.53	16.8± 0.67	17.9± 0.78	18.5± 0.33	20.1± 1.56	22±2.23	22.6± 2.9
2	26± 0.56	27± 01.5	26.8± 1.4	25.9± 1.8	24.7± 1.5	26.5± 0.98	26.3± 1.23	27±2.3	29.9± 1.78	30.2± 2.2
3	35.6± 2.1	37.3± 0.79	38.6± 1.6	34.7± 1.2	38.4± 2.1	39.3± 2.2	40.4± 1.7	42.7± 1.4	43.5± 1.5	44.7± 1.3
4	47.4 ± 1.81	50.2 ± 2.18	51.1 ± 2.37	44.2 ± 1.74	46.8 ± 1.51	48.3 ± 2.54	55.6 ± 1.91	58.3 ± 2.14	61.7 ± 2.36	62.1 ± 2.09
6	58.2 ± 2.78	60.1 ± 2.36	62.5 ± 1.84	50.5 ± 1.85	55.9 ± 2.80	59.7 ± 2.86	62.4 ± 2.78	68.6 ± 1.81	74.5 ± 2.48	74.2 ± 2.35
8	75.4 ± 2.81	77.9 ± 2.51	77.3 ± 1.25	70.5 ± 1.39	72.3 ±1.15	75.3 ± 2.87	81.4 ± 2.44	83.3 ± 2.34	86.9 ± 1.46	86.9 ± 1.12
10	85.3 ± 2.42	88.4 ± 2.18	89.7 ± 1.61	75.4 ± 2.15	79.6 ±1.89	84.6 ± 2.22	89.7 ± 2.28	90.1 ± 2.81	91.2 ± 2.93	91.4 ± 2.65
12	98.6 ± 1.87	98.9 ± 2.59	99.2 ± 1.56	88.4 ± 2.69	90.7 ± 1.98	92.8 ± 2.29	98.6 ± 2.08	99.7 ± 2.25	99.9 ± 1.47	98.8 ± 2.29

All values are expressed as mean ± standard deviation

CONCLUSION

Bilayer tablets are able to provide multiple releases kinetic of same/different drug. It is preferred to co-administer two different drugs in the same dosage form and controlling drug release rate of two different API. It is also preferred to reduce of pill burden and safety margin of high potency drug can be increased. For prepared immediate layer was evaluated for weight variation, thickness, hardness, friability, DT, WT, drug content, dissolution. Among the total 10 batches F2 has been satisfied above all criteria. For prepared sustained release layer was evaluated for weight variation, thickness, hardness, friability, disintegration time, drug content and % cumulative drug release. Among the all 10 batches (F1-F10), F6 has been satisfied above all the evaluation criteria.

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CONFLICT OF INTEREST

The entire author's declared as no conflict of interests.

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