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A COMPARATIVE DISSOLUTION STUDY OF COMBINATION DOSE OF PARACETAMOL (500mg) AND IBUPROFEN (200 mg): FORMULATION ASPECTS OF SOLID DOSAGE FORMS AVAILABLE IN BANGLADESH

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Abstract:

This paper reports a study has been designed to formulate and to offer a comparison of various parameters of combination dose of Paracetamol (500 mg) and Ibuprofen (200 mg). A combined solid dosage form of Paracetamol (500mg) and Ibuprofen (200mg) is formulated and tested by analytical parameters.We use Nuromol (Paracetamol 500 mg and Ibuprofen 200 mg; Reckitt Benckiser Healthcare, UK) as a vendor drug for the purpose to cure from mild to moderately severe pain as a new combination dosage regimen in Bangladesh. Initially combined dosage regimen was prepared using six different formulas and formulated drugs are tested for checking all parameters as with supplied reference drugs. The assay is carried out by employing HPLC system with UV detection at 222 nm.There after each formulation had been subjected to preformulation and postformulation studies. The tablet mass is evaluated by assessing various compressional parameter such as angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index. All the results are met the specifications and this results indicated that this new formulation have good flow properties. Various kinetic models were employed for the application of in vitro release profile assessment. The hardness of the tablet is found 4.3 to 6 kg, friability of the tablet is found 0.25 to 0.63%, disintegration time for the core tablet and the coated tablet are found 40 seconds and 1.30 seconds respectively. The results also show that the presence of active components in the formulated tablets are 100.31% Paracetamol and 101.12% Ibuprofen. We observed the potencies of the Paracetamol are 103.36% and 99.29% for Ibuprofen. All results of post formulation parameters were according to pharmacopoeias and within acceptable range. Based on fundamental comparative behavior of drug dissolution it can be concluded that release profile of all six batches under investigation was compatible with reference drug. In this present study as the newly formulated combination dosages regimen has met all the acceptance criteria and complied with the pharmacopoeial specifications and reference standard this formulation can be adapted as commercial preparation in Bangladesh for treatment of mild to moderately severe pain for post-operative patients.

Key words: *Formulation approach of dosages regimen, Parameters testing, In vitro release, Comparative dissolution profile, Treatment indication, Commercial approach.*

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INTRODUCTION:

Pain is a common and growing problem in our societies [1]. It may occur intentionally or unintentionally. The relief of pain has been described as a universal human right but is not always easily achieved [2]. Generally it is a common scenario in Bangladesh for physicians to prescribe some locally available painkillers or analgesics such as Aceclofenac, Diclofenac, Naproxan, Ketorolac, Paracetamol (acetaminophen), Ibuprofen etc for curing mild to moderately severe pain. These drugs produce gastrointestinal upset that also may include gastric ulceration/bleeding. That is why to counter these adverse effects additional drugs are prescribed. Paracetamol and Ibuprofen are more frequently prescribed as these are effective anti-inflammatory, analgesic and antipyretic medicine with considerably less gastrointestinal adverse effect than other NSAIDs [3-5]. Prescribing Acetaminophen and Ibuprofen together is common in clinical practice [6-11]. Paracetamol also known as acetaminophen or APAP, chemically named N-acetyl-p-aminophenol, is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer) [12-13]. Acetaminophen is widely used and is very safe at the recommended dose of 4g per day [14]. The mode of action of Paracetamol is not completely understood, but appears to be related to the inhibition of a subclass of cyclooxygenase enzyme isoforms in the central nervous system [15]. Ibuprofen is the most commonly used and most frequently prescribed NSAID [16-17]. It is a non-selective inhibitor of cyclo-oxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) [18]. Ibuprofen is supplied as tablet with a potency of 200 to 800mg [19]. Ibuprofen has the advantage of a well-established safety record (particularly at doses below 1.5 g per day in adult) [20]. Combination of ibuprofen and paracetamol (200/500 mg) tablet is frequently indicated for temporary relief of mild to moderate pain associated with migraine, headache, back-ache, period pain, dental pain, rheumatic and muscular pain, non-serious arthritis pain, cold and flu symptoms, sore throat, and fever [21]. This product is especially suitable for pain that requires stronger analgesia than ibuprofen or paracetamol alone [22]. A small study on the pharmacokinetic properties of ibuprofen and paracetamol, when taken concurrently, found no significant change in kinetic parameters of the two drugs [23]. Paracetamol and ibuprofen are absorbed rapidly after oral administration [24]. Paracetamol and ibuprofen are metabolized in the liver and excreted by kidney.

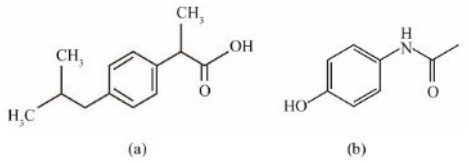


Fig. 1: **Chemical structure of (a) Paracetamol and (b) Ibuprofen.**

Furthermore, Paracetamol is observed to provide less effective analgesia than NSAIDs in some indications such as dental pain and sore throat [26-27]. For the relief of more severe pain, combination analgesia is often recommended, as the combination of analgesics with different modes of action has the potential to offer enhanced pain relief with a comparatively lower dose of each analgesic and corresponding reduced side effects [28]. Ibuprofen and paracetamol are frequently used in combination in clinical practice and are available as a fixed dose combination tablet over-the-counter in some countries [29]. In UK, Nuromol (Para500mg/Ibu200mg) and Mexigesic (Para500mg/Ibu200mg) are available for the treatment of pain. But in Bangladesh there have no use of this combination dose but they are widely used individually. This present work was conducted to formulate and comparative study of various parameters of combination dose of Paracetamol (500mg) and Ibuprofen (200mg) using Nuromol (Paracetamol 500mg and Iboprofen 200mg; Reckitt Benckiser Healthcare, UK) as model/ vendor drug for the purpose of the treatment of mild to moderately severe pain as a new combination dosage regimen in Bangladesh.

METHODS AND MATERIALS:

Study design and objective

This study was designed into two segments. Firstly, formulation of combined dose of Paracetamol and Ibuprofen (500 mg/200 mg) according to the United States Patent Application Publication (Pub.No.: US2011/0275718 A1) and European Patent Specification (Pub.No.: EP1781277 B1) which has been designed by Hartley Campbell Atkinson [30,31]. Secondly comparision of various parameters using Nuromol (Paracetamol 500mg and Ibuprofen 200mg; Reckitt Benckiser Healthcare, UK) as model/ vendor drug. The objective of this study was to formulate Paracetamol and Ibuprofen (500mg/200mg) combined immediate release tablet dosage form for the purpose of the treatment of mild

to moderately severe pain as a new combination dosage regimen in Bangladesh.

Machines and Apparatus

Table 1: Name of the equipments with their brand name and source.

Name of Equipments	Brand Name	Source
Electronic balance	Sartorious	Germany
Compression machine	Shimadzu	Japan
Disintegration tester	Pharmachine	India
Dissolution tester	Electrolab	Germany
HPLC machine	Dionex	California, USA

Drugs, Excipients and Chemicals

The API Paracetamol (Pharmatech, Bangladesh) and Ibuprofen (IOL Chemical, India) were collected. The others ingredients or excipients such as Avicel-101 and Croscarmellose sodium (Mingtai Chemicals, Taiwan), Maize starch (Samyung Genex, Korea), Methyl paraben and Propyl paraben (San Fu Chemicals Ltd. Taiwan), Purified talc (Fuji Kajei co. Ltd. Japan), Aerosil 200 (Evonik Industries Ltd. Germany), Magnesium stearate (Perter Greven, Nederland) and other chemicals such as Potassium dihydrogen orthophosphate (source; Germany), Sodium hydroxide (source; Germany), HPLC grade acetonitrile (source; Bangladesh), diluted phosphoric acid (source; Germany), dipotassium hydrogen phosphate (source; England) were obtained from Navana Pharmaceuticals Limited, Bangladesh. All the chemicals and reagents were of analytical grade.

Tablet preparation by wet granulation technique

The Paracetamol (500mg) and Ibuprofen (200mg) film coated immediate release solid tablet has been prepared by wet granulation method according to the United States Patent Application Publication (Pub.No.: US2011/0275718 A1) and European Patent Specification (Pub.No.: EP1781277 B1) which has been designed by Hartley Campbell Atkinson [30,31]. Here Pharmachine 8 station compression machine (source; India, 16.5 mm punch and 16.5 mm die) was used.

Study of physical parameters evaluation of the formulated tablets

Pre-compression evaluation: Before compression granules are subjected for evaluation using various parameters like angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index according to the methods of USP29-NF24.

Post-compression evaluation:

The size and shape of the tablets were determined according to dimensions during compression. Tablet thickness and diameter were determined by a digital slide calipers. The weight variation was regulated by taking 10 tablets within an Electronic analytical balance (AY220, Shimadzu, Japan) and sample tablets were collected from each batch to evaluate the weight variation among them. We also calculated the mean and the standard deviation (USP30-NF25) to find more accuracy. The hardness of 10 tablets were governed by the hardness tester (Monsanto Hardness Tester) (USP29-NF24). Tablets friability was controlled and determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics) for 4 minutes at 25 rpm (USP29-NF25). We carried out a disintegration test using disintegration tester (Electrolab, made in India) at 37 ± 0.5°C temperature (USP29-NF25).

Dissolution test of formulated tablet

Dissolution test was performed by paddle method. Dissolution medium (0.2 M Potassium buffer pH 7.2) and other dissolution conditions were used according to previously reported work of Zareena *et al.*, 2013 [32]. Tablets were dropped vessels of dissolution apparatus USP type II (Electrolab dissolution tester, India) containing dissolution medium at 37.1ºC. The dissolution apparatus was allowed to run for 60 min and samples were collected at 5 minutes interval and analyzed to study dissolution profile at HPLC system. The % release of Paracetamol (500mg) and Ibuprofen (200mg) from the tablets were calculated.

Assay test of the formulated tablet

The assay test of the formulated tablet was conducted according to the previously reported work of Asma *et al*. 2014 [33] by using HPLC system (Dionex HPLC system, California), equipped with an auto sampler (Model—Ultimate 3000) and UV– visible detector (Model—SPD 20A), was used for the analysis. The data were recorded using LC-solution software. Analytical RP C18 column [NC – 250 mm × 4.6 mm. company prontosil, 5 µ, Phenomenex Inc.] was used to analyze the standard and samples.

Potency test for the formulated tablet

The potency of the formulated tablet was determined according to the previously reported work of Asma *et al*. 2014 [33]. Potency test was conducted by

introducing six tablets in each of the vessel containing dissolution medium of dissolution tester and it was allowed to run for one hour. Then samples were withdrawn and analyzed in HPLC system in same condition like assay test against standard solution of Paracetamol and Ibuprofen.

Comparative dissolution test study

The dissolution rate of the formulated tablet was compared with the vendor drug Nuromol tablet in terms of similarity Factor (f_2) [34]. For this purpose Nuromol tablet was collected from UK and the dissolution of this product was studied for 1 hour in the same condition of the test sample. Similarity Factor (f_2) was determined by the following equation:

$$f_2 = 50\log X \left[\frac{100}{\sqrt{1 + \frac{\sum_{t-1}^{t-n} (\overline{R}t - \overline{T}t)^2}{n}}} \right]$$

Where Rt and Tt are dissolution at time point t of the vendor/innovator and test sample respectively, n is the number of sampling time.

Stability Study

Paracetamol (500mg) and Ibuprofen (200mg) combined formulated tablets were subjected to accelerated stability condition to check stability profile for three months, packaged in aluminum foil to prevent the formulation from exposure to light to simulate the aluminum packaging. Stability study of formulated tablets were performed as tablet dosage form in Aluminum-PVDC packaging mode at accelerated condition for three months. Samples were withdrawn after one month interval and evaluated for change in size, shape, color, hardness, friability, in-vitro drug release pattern and drug content.

Table 2: Stability test condition with minimum time period

Study	Study condition	Minimum time period
Long term	25±2ºC/60±5%RH or	6 months (option 1)
	30±2ºC/65±5%RH	12 months (option 2)
Intermediate	30±2ºC/65±5%RH	6 months
Accelerated	40±2ºC/75±5%RH	6 months

RESULTS:

Parameters test result of formulated tablet

The pre-compressional parameters of the tablet mass was assessed and it has been reported in Table 3. We observe from this table that all parameters meet standard specifications. All the post-compressional parameters are within the acceptable range and comply with the pharmacopoeial specifications as shown in Table 4. In the stability study, we also observed that after three months the color, size and shape remained same as initial for both long term and intermediate conditions. The color and shape of the tablets were slightly changed in accelerated conditions and in this case some tablets become brownish as reported in Table 5.

Table 3: Result of granules evaluation

Pre-compressional parameters	Results	Experimental specifications
Angle of repose- (°)	32.47	If 31-35,then good flow property
Bulk density- (g/ml)	0.35	-
Tapped density- (g/ml)	0.41	-
Compressibility (Carr's) index-(%)	14.6	If range 11-15, then good compressibility and flow ability
Hausner ratio	1.17	If range 1.12-1.18, then good flow ability

Table 4: Result of the tablet evaluation

Post-compressional parameters	Experimental specifications	Results (Mean±SD)
General appearance, shape and organoleptic properties	White, smooth tablets without objectionable smell	White, caplet shape and smooth film coated tablets. No objectionable smell was found.
Size and shape	Tablet size should be patient compliant	Caplet shape tablet with thickness-5.5 ± 0.62, length-15.85 ± 0.0069, Width- 8.73 ± 0.009
Weight variation (mg) (n=10)	Prescribed limit ± 5% for tablets weighing more than 300 mg	830.71 ± 1.43
Hardness(kg/cm^2) (n=10)	For film coated tablet 4-10 kg	5.3 ± 0.54
Friability (%) (n=3)	Not more than 1%	0.41± 0.2
Disintegration time (min) (n=3)	Not more than 15 minutes	Core tablet: 39.67 sec ± 1.53
		Coated tablet: 1min 30sec ± 0.15
Assay test	± 15% of label claim	100.31% for Paaracetamol and 101.12% for Ibuprofen
Potency	Within the range of 90.0% to 110.0%.	103.36% for Paracetamol and 99.29% for Ibuprofen

Table 5: Appearance of tablets at different time intervals during stability study.

Initial	No temperature	White in color and caplet shape tablet
Zero month	25±2ºC/60±5%RH	Color as initial and shape is uniform
	30±2ºC/65±5%RH	Color as initial and shape is uniform
	40±2ºC/75±5%RH	Color as initial and shape is uniform
After one month	25±2ºC/60±5%RH	Color as initial and shape is uniform
	30±2ºC/65±5%RH	Color as initial and shape is uniform
	40±2ºC/75±5%RH	Some tablets become slightly brown
After two months	25±2ºC/60±5%RH	Color as initial and shape is uniform
	30±2ºC/65±5%RH	Color as initial but shape is not uniform
	40±2ºC/75±5%RH	Tablets become brown
After three months	25±2ºC/60±5%RH	Color as initial but shape is not uniform
	30±2ºC/65±5%RH	Tablets become brown and is not uniform
	40±2ºC/75±5%RH	Tablets become brownish

Table 6: Release pattern of Paracetamol and Ibuprofen (500 mg and 200 mg) immediate release tablet at different times (5 minutes interval).

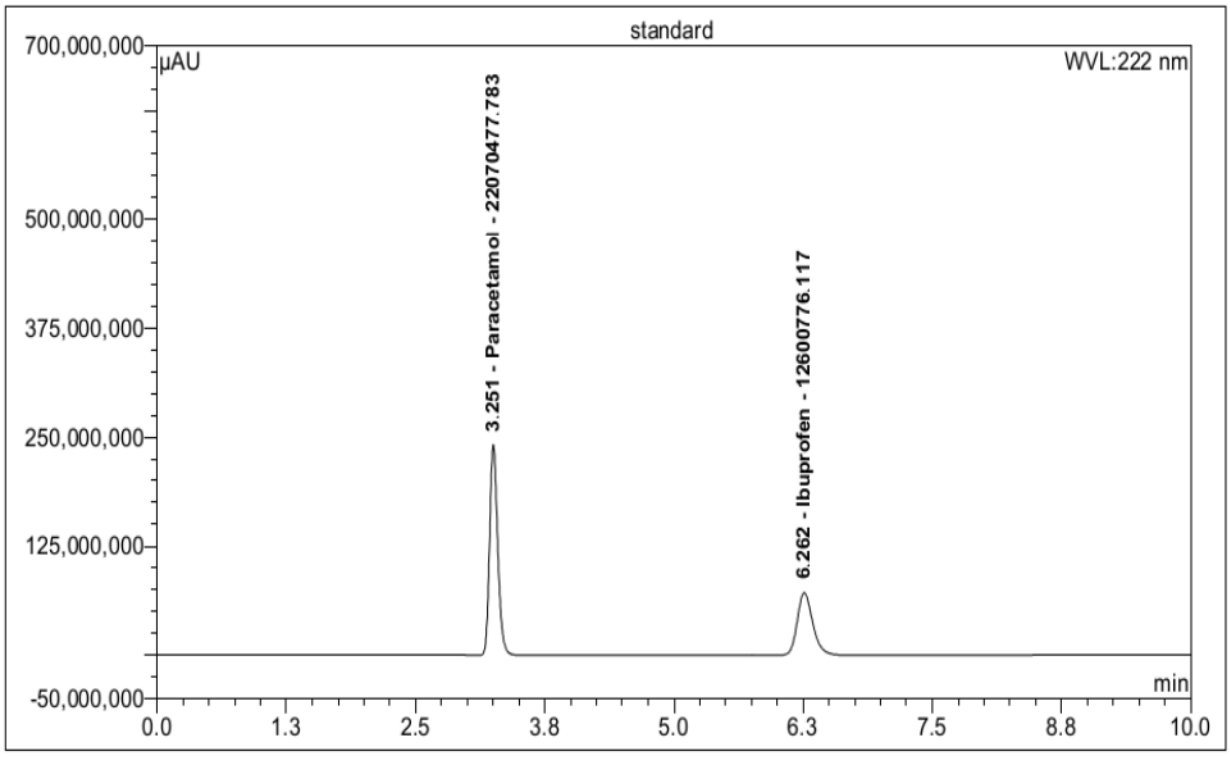
Release (%) of paracetamol and ibuprofen of formulated tablet at 5 mins interval to 1 hour	**Ingredients**	
	Paracetamol	**Ibuprofen**
Release after 5 minutes (%)	35.01%	22.89%
Release after 10 minutes (%)	41.34%	30.00%
Release after 15 minutes (%)	47.00%	36.67%
Release after 20 minutes (%)	55.09%	42.60%
Release after 25 minutes (%)	63.69%	49.00%
Release after 30 minutes (%)	69.45%	56.00%
Release after 35 minutes (%)	75.45%	63.90%
Release after 40 minutes (%)	82.00%	69.87%
Release after 45 minutes (%)	87.67%	76.00%
Release after 50 minutes (%)	93.49%	83.34%
Release after 55 minutes (%)	98.34%	90.55%
Release after 60 minutes (%)	102.02%	96.12%

Dissolution Test Result

The dissolution profile of the combined solid dosage form of Paracetamol (500mg) and Ibuprofen (200mg) tablets were evaluated as the percentage of drug released at 5 minutes interval for 1 hour shown in Table 6. These studies show that approximately 50% of the drug is released from the formulated tablet within 25 minutes and within 1hour, almost 100% of the drug is released

Result of Assay Test

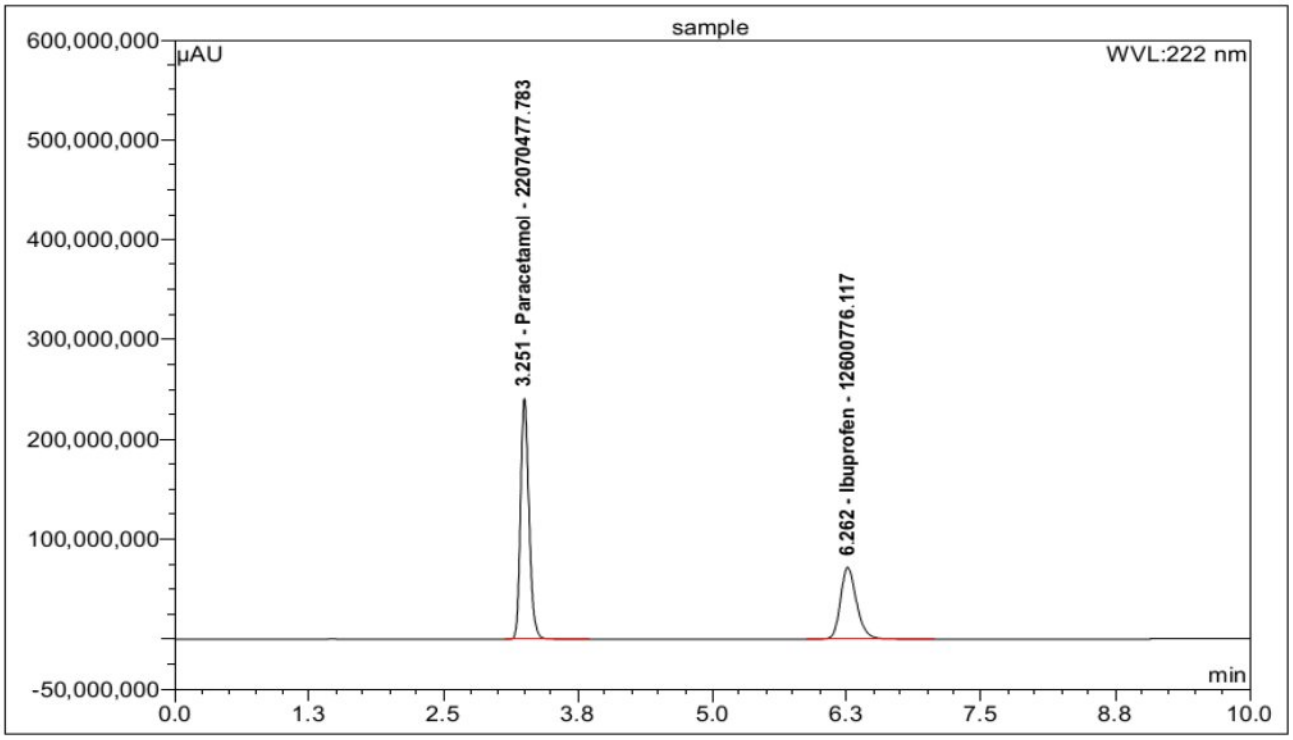
The assay test was conducted to find out the presence of active component. The result show the presence of 100.31% Paracetamol and 101.12% Ibuprofen in the formulated combined dosage form. As according to the pharmacopoeial specification, drug content in tablet should be ± 15% of label claim, so the new product meet this criteria. The chromatogram and data from HPLC of Standard and sample of Paracetamol 500 mg and Ibuprofen 200 mg obtained for drug content or assay determination are given in Fig-2 and Fig-3 respectively.



Sample No	Sample Name	Ret.Time	Area	Height	Asymmetry(EP)	Plates(EP)
		min	µAU*min	µAU		
		Paracetamol	Paracetamol	Paracetamol	Paracetamol	Paracetamol
		UV_VIS_1	UV_VIS_1	UV_VIS_1	UV_VIS_1	UV_VIS_1
1	Standard	3.25	22085544.233	237763720.000	1.23	8211
2	Standard	3.25	22111616.883	240862340.000	1.19	8426
3	Standard	3.25	22302949.933	239211560.000	1.21	8163
	Average:	3.249	22166703.7	239279206.7	1.2	8266.667
	Rel.Std.Dev:	0.059 %	0.536 %	0.648 %	1.631 %	1.694 %

Sample No	Sample Name	Ret.Time	Area	Height	Asymmetry(EP)	Plates(EP)
		min	µAU*min	µAU		
		Ibuprofen	Ibuprofen	Ibuprofen	Ibuprofen	Ibuprofen
		UV_VIS_1	UV_VIS_1	UV_VIS_1	UV_VIS_1	UV_VIS_1
1	Standard	6.27	13920465.433	78760260.000	1.23	8570
2	Standard	6.26	13900054.567	79256640.000	1.24	8687
3	Standard	6.26	14022856.700	79623300.000	1.25	8587
	Average:	6.266	13947792.2	79213400.0	1.2	8614.667
	Rel.Std.Dev:	0.111 %	0.472 %	0.547 %	0.912 %	0.734 %

Fig. 2: The chromatogram and HPLC data of standard Paracetamol and Ibuprofen for assay test.



Sample No	Sample Name	Ret.Time min Paracetamol UV_VIS_1	Area µAU*min Paracetamol UV_VIS_1	Height µAU Paracetamol UV_VIS_1	Weight	Amount Paracetamol UV_VIS_1
4	Paracetamol and Ibupro	3.25	21983865.767	240995120.000	1.0000	0.1684
5	Paracetamol and Ibupro	3.25	21981402.833	237584230.000	1.0000	0.1683
6	Paracetamol and Ibupro	3.25	22070477.783	241520230.000	1.0000	0.1690
	Average:	3.253	22011915.5	240033193.3	1.0	0.169
	Rel.Std.Dev:	0.000 %	0.230 %	0.890 %	0.000 %	0.230 %

Sample No	Sample Name	Ret.Time min Ibuprofen UV_VIS_1	Area µAU*min Ibuprofen UV_VIS_1	Height µAU Ibuprofen UV_VIS_1	Weight	Amount Ibuprofen UV_VIS_1
4	Paracetamol and Ibupro	6.27	12538658.567	71675540.000	1.0000	0.2124
5	Paracetamol and Ibupro	6.26	12570291.233	71327600.000	1.0000	0.2129
6	Paracetamol and Ibupro	6.26	12600776.117	72030450.000	1.0000	0.2134
	Average:	6.263	12569908.6	71677863.3	1.0	0.213
	Rel.Std.Dev:	0.092 %	0.247 %	0.490 %	0.000 %	0.247 %

Fig. 3: The chromatogram and HPLC data of sample Paracetamol and Ibuprofen for assay test.

Result of Potency Test

The potency of Paracetamol (500 mg) and Ibuprofen (200 mg) was evaluated by using six samples of formulated tablet and the potency of six samples is shown in Fig-4. The average potency for Paracetamol is 103.36% and 99.29% for Ibuprofen. As the potency should be within the range of 90.0% to 110.0% so this potency of the formulated tablet met the specification. The chromatogram and data from HPLC of Standard and sample of Paracetamol 500 mg and Ibuprofen 200 mg obtained for potency determination are given in Fig-2 and Fig-3 respectively.

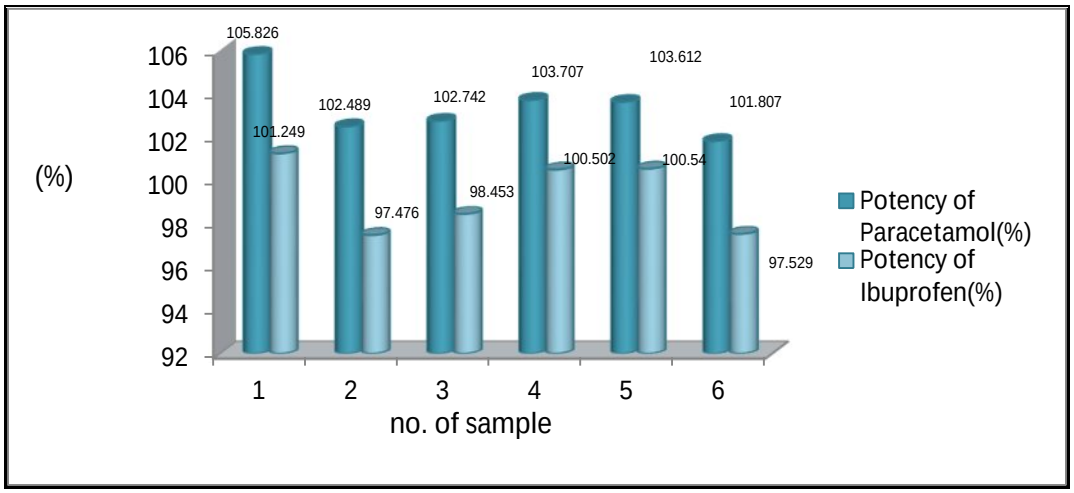
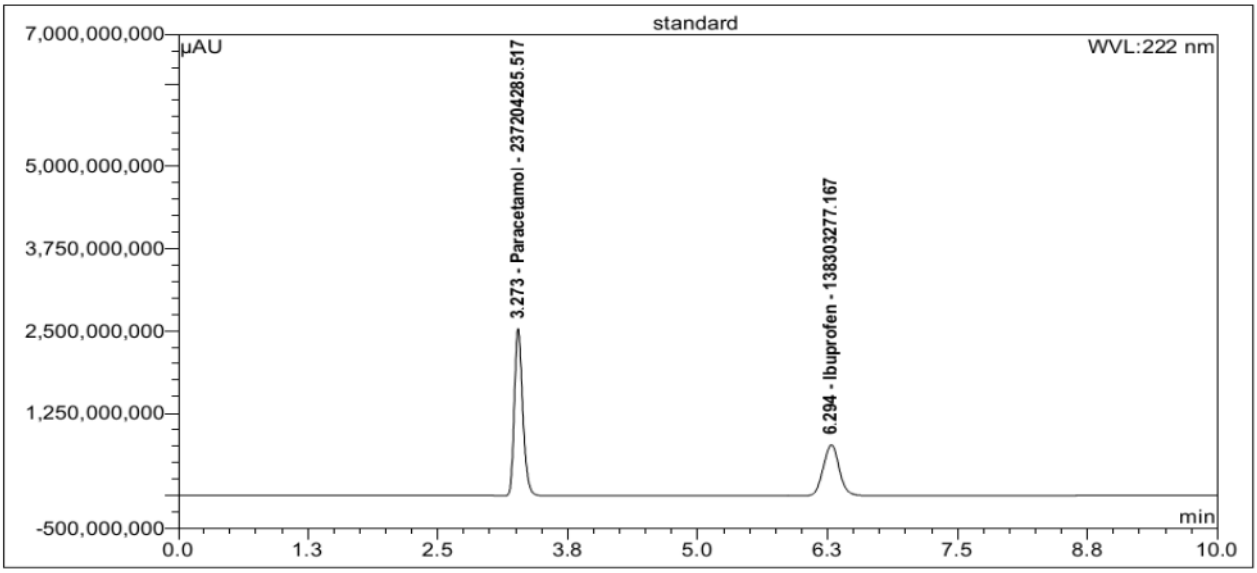


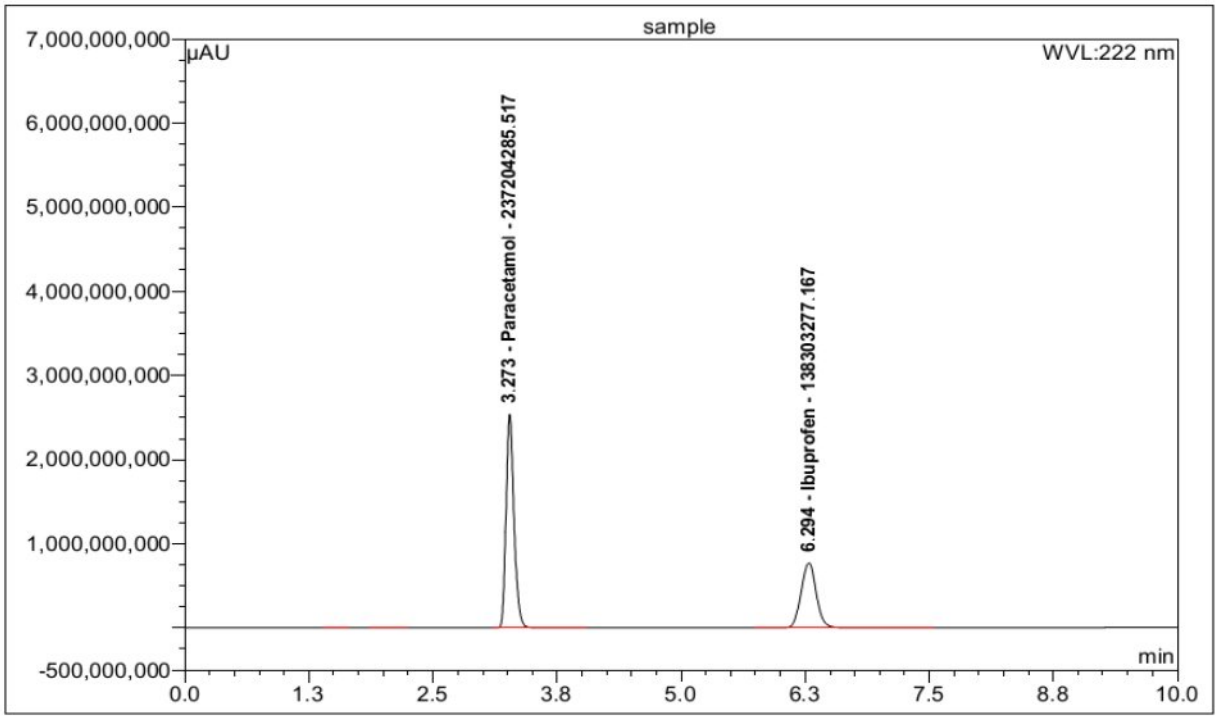
Fig. 4: Graphical presentation of potency test result of formulated tablet.



Sample No	Sample Name	Ret.Time	Area	Height	Asymmetry(EP)	Plates(EP)
		min	µAU*min	µAU		
		Paracetamol	Paracetamol	Paracetamol	Paracetamol	Paracetamol
		UV_VIS_1	UV_VIS_1	UV_VIS_1	UV_VIS_1	UV_VIS_1
7	Std disso	3.25	213135679.000	2272026860.000	1.25	8051
8	Std disso	3.27	213665091.500	2292051820.000	1.25	8247
9	Std disso	3.27	213529782.433	2292858710.000	1.23	8296
	Average:	3.261	213443517.6	2285645796.7	1.2	8198.000
	Rel.Std.Dev:	0.387 %	0.129 %	0.516 %	0.739 %	1.581 %

Sample No	Sample Name	Ret.Time	Area	Height	Asymmetry(EP)	Plates(EP)
		min	µAU*min	µAU		
		Ibuprofen	Ibuprofen	Ibuprofen	Ibuprofen	Ibuprofen
		UV_VIS_1	UV_VIS_1	UV_VIS_1	UV_VIS_1	UV_VIS_1
7	Std disso	6.16	123644364.633	694486090.000	1.08	7887
8	Std disso	6.25	123746173.467	701559200.000	1.09	8297
9	Std disso	6.27	123719112.100	701389730.000	1.09	8350
	Average:	6.226	123703216.7	699145006.7	1.1	8178.000
	Rel.Std.Dev:	0.972 %	0.043 %	0.577 %	0.480 %	3.099 %

Fig. 5: The chromatogram and HPLC data of standard Paracetamol and Ibuprofen for potency test.



Sample No	Sample Name	Ret.Time	Area	Height	Weight	Amount
		min	µAU*min	µAU		
		Paracetamol	Paracetamol	Paracetamol		Paracetamol
		UV_VIS_1	UV_VIS_1	UV_VIS_1		UV_VIS_1
10	Spl 1	3.27	244326312.683	2630503780.000	1.0000	n.a.
11	Spl 2	3.27	236621481.367	2534700410.000	1.0000	n.a.
12	Spl 3	3.27	237204285.517	2542051060.000	1.0000	n.a.
13	Spl 4	3.27	239433373.733	2567856580.000	1.0000	n.a.
14	Spl 5	3.28	239214633.267	2565228030.000	1.0000	n.a.
15	Spl 6	3.28	235045376.567	2524340490.000	1.0000	n.a.
	Average:	3.273	238640910.5	2560780058.3	1.0	#DIV/0!
	Rel.Std.Dev:	0.129 %	1.356 %	1.491 %	0.000 %	#DIV/0!

Sample No	Sample Name	Ret.Time	Area	Height	Weight	Amount
		min	µAU*min	µAU		
		Ibuprofen	Ibuprofen	Ibuprofen		Ibuprofen
		UV_VIS_1	UV_VIS_1	UV_VIS_1		UV_VIS_1
10	Spl 1	6.29	142231547.650	793662110.000	1.0000	n.a.
11	Spl 2	6.29	136929857.733	769225810.000	1.0000	n.a.
12	Spl 3	6.29	138303277.167	774019520.000	1.0000	n.a.
13	Spl 4	6.29	141181761.850	789686840.000	1.0000	n.a.
14	Spl 5	6.30	141234562.800	788748340.000	1.0000	n.a.
15	Spl 6	6.31	137005269.583	765230670.000	1.0000	n.a.
	Average:	6.294	139481046.1	780095548.3	1.0	#DIV/0!
	Rel.Std.Dev:	0.159 %	1.683 %	1.546 %	0.000 %	#DIV/0!

Fig. 6: The chromatogram and HPLC data of sample Paracetamol and Ibuprofen for potency test.

Comparative dissolution study between vendor (Nuromol) tablet and formulated immediate release tablet

Comparative dissolution study was performed between vendor product and test product.

Here,

Vendor product= Nuromol (paracetamol 500mg and ibuprofen 200 mg).

Test product = Formulated paracetamol 500mg and ibuprofen 200mg combined immediate release tablet

The formulated tablet met the range of comparative dissolution study which is 50 or more than 50 shown in Fig-7.

f_2 factor calculation for Paracetamol

f_2 factor of Paracetamol was found 50.00 which is comply with standard range of 50 or >50.

Time Point	010P2E	010P4E
0 min	0	0
15. min	82	88
30 min	97	89
45 min	99	89
60 min	105	91

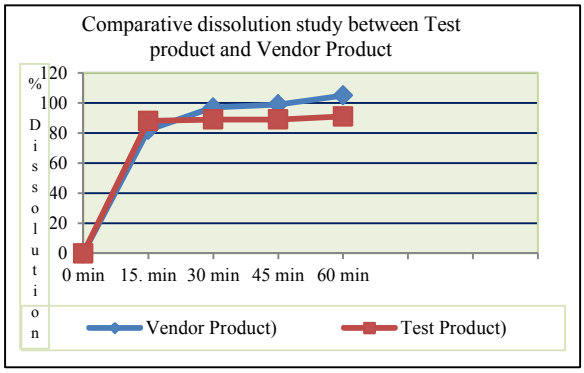


Fig. 7: Graphical presentation of comparative dissolution study between test product and vendor product.

f_2 factor calculation for Ibuprofen

f_2 factor of Ibuprofen was found 50.39 which is comply with standard range of 50 or >50.

Time Point	010P2E	010P4E
0 min	0	0
15. min	92	86
30 min	96	87
45 min	97	86
60 min	99	87

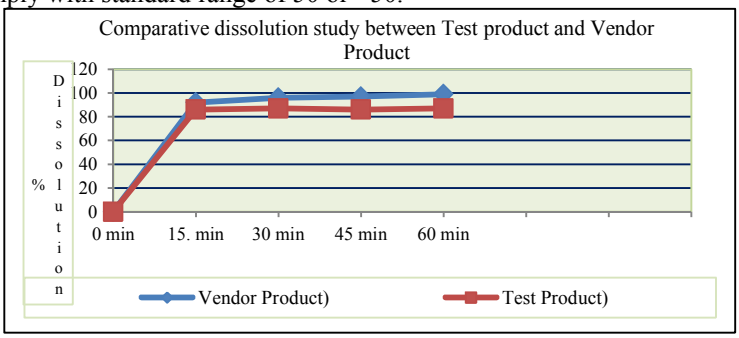


Fig. 8: Graphical presentation of comparative dissolution study between test product and vendor product.

Comparative release pattern study of Vendor (Nuromol) and proposed formulated tablet (test product)

Percentage release of Paracetamol and Ibuprofen (vendor product) after 1 hour was 105 and 99 respectively. Graphical presentation of percentage release profile of Paracetamol and Ibuprofen (vendor) is shown in Fig-9 and Fig-10. The percentage release of Paracetamol and Ibuprofen (test product) after 1 hour was 91% and 87% respectively is shown in Fig-11 and Fig-12.

Percentage release profile of vendor (Nuromol) product

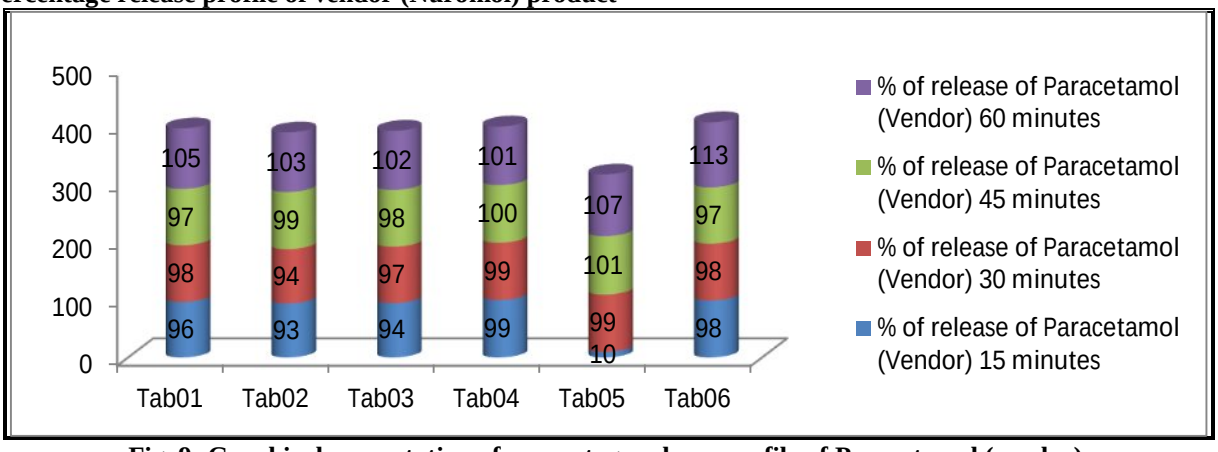


Fig. 9: Graphical presentation of percentage release profile of Paracetamol (vendor).

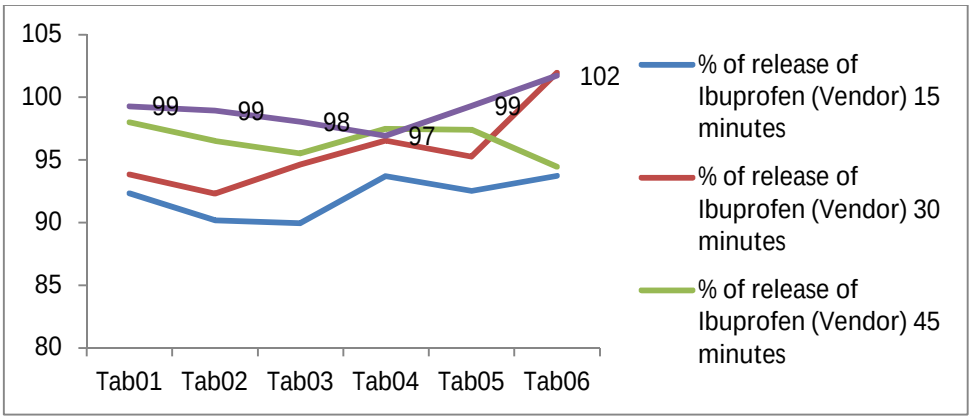


Fig. 10: Graphical presentation of % release profile of Ibuprofen (vendor).

Percentage (%) release profile of formulated tablet (test product)

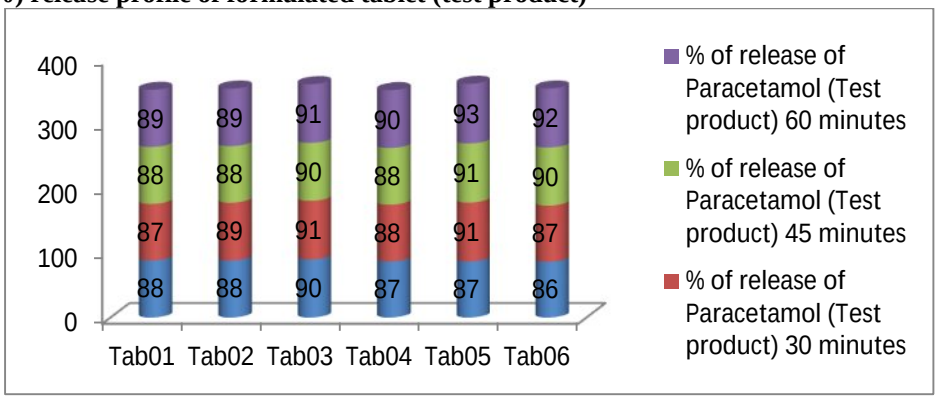


Fig. 11: Graphical presentation of percentage release profile of Paracetamol (test product).

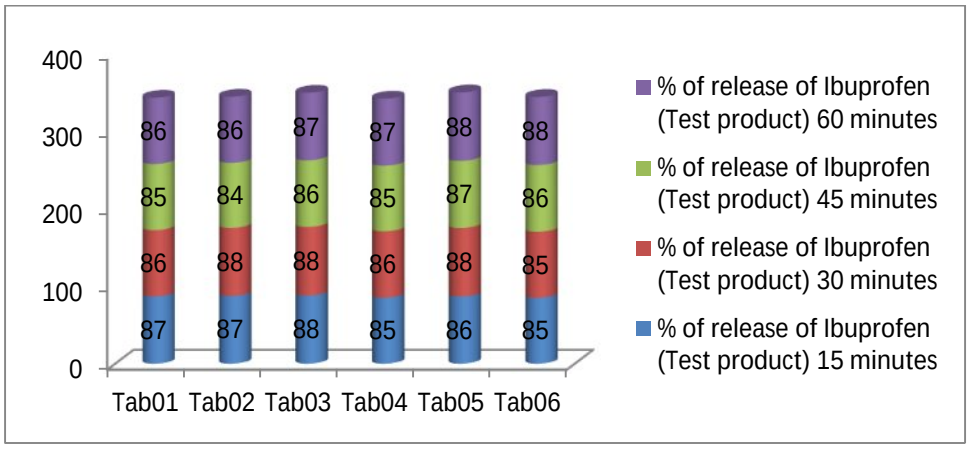


Fig. 12: Graphical presentation of percentage release profile of Ibuprofen (test product).

DISCUSSION:

The evaluation of tablet was conducted in two stages. These stages were pre-compression evaluation and post-compression evaluation. The granules were evaluated before compression by using angle of repose, bulk density, tapped density, hausner's ratio and compressibility index. The angle of the repose of the granules was found 32.47^0 showed good flow property of granules during compression. Hausner ratio of 1.17and Carr's index of 14.6% were estimated by using values of bulk and tapped densities respectively and given in Table 2 which met standard specifications. All the post-compressional parameters were within the acceptable range and

complied with the pharmacopoeial specifications. The weight variation of the tablet was found 0.15 to 0.34% and the range is ±5%. The mechanical strength of tablets is often defined as the force required fracturing a tablet across its diameter [35]. The hardness of the tablet was found 4.3 to 6 kg and the range is 4 to 8 kg, or 10 kg and NLT 3kg. The friability of the tablet was found 0.25 to 0.63% as the tablet was coated and the range is NMT 1%. The disintegration time of the core tablet was found 40sec. and the coated tablets were 1.30sec. The acceptance criteria of the core tablet is NMT 15 minutes and for coated tablet is NMT 60 minutes. The moisture content of tablet was found 2.1 to 2.7% and the range is 2-3%. The dissolution test was performed to determine the % of release of drug. Dissolution testing of solid oral drug products has emerged as one of the most important control tests for assuring product uniformity and batch-to-batch equivalence [34, 36]. After 60 minutes the % release of Paracetamol was found 102.02% and the % release of Ibuprofen was found 96.12% and the range is NLT 70% after 60 minutes. The analytical parameters tests were conducted by HPLC system. The assay test was conducted and showed the presence of active components, Paracetamol and Ibuprofen was found respectively 100.31% and 101.12% and the range is 90% to 110%. So the assay of the tablet is compatible. The potency of the of the six sample of Paracetamol of the tablet were found respectively 105.826%, 102.489%, 102.742%, 103.707% 103.612% 101.807% and the Ibuprofen were found respectively 101.249%, 97.476%, 98.453%, 100.502%, 100.54%, 97.529%. This potency were in the acceptable range. So the potency of the tablet is compatible. The accelerated stability study was performed of the formulated tablet. The formulated tablet was subjected to accelerated stability condition to check stability profile for three months. The major aim of pharmaceutical stability testing is to provide reasonable assurance that the products will remain at an acceptable level of fitness/quality throughout the period during which they are in market place available for supply to the patients and will be fit for their consumption until the patient uses the last unit of the product [37]. After stability testing the color, size and shape were remain same as initial at long term and intermediate condition. The color and shape of the tablets were slightly changed in accelerated conditions and in this case some tablets become brown. The analytical test were also performed of accelerated stability testing tablet and all the test results were met the previous test results. The % release of test product was compared with the vendor drug (Nuromol). These release patterns of the test product were compared with the innovator/vendor drug in the term of similarity factor (f_2). If the similarity factor (f_2) is more then 50 than the test product will be compatible. The f_2 factor of the Paracetamol was found 50.00 and Ibuprofen was found 50.39. So it is compatible. The percentage (%) of release of vendor Paracetamol were found averagely 82%, 97%, 99%, 105% and Ibuprofen 92%, 96%, 97%, 99%. These results met the criteria. The percentage (%) release of test Paracetamol were found 88%, 89%, 89%, 91% and Ibuprofen 86%, 87%, 86%, 87%. These results also met the acceptable criteria.

CONCLUSION:

In the present study, Paracetamol (500mg) and Ibuprofen (200mg) combined tablet has been formulated by employing wet granulation method and all pre-compression and post-compression tests have been conducted to evaluate the formulated tablet. This study shows all the test results meet the pharmacopoeial specifications. These results also show that this test product is compatible. Since this newly formulated combination dosages regimen meets all criteria with reference standard, this formulation can be adapted as commercial preparation in Bangladesh for treatment of mild to moderately severe pain after post-operative patients.

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