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Formulation and Evaluation of Effervescent Tablet of Paracetamol and Ibuprofen

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ABSTRACT

Recently, fast-dissolving drug delivery system have started gaining popularity and acceptance as new drug delivery system, because they are easy to administer and lead to better compliance. Usually, elderly people experience difficulty in swallowing the tablet. Paracetamol having analgesic, antipyretic effect, they inhibit cyclooxygenase enzyme involved in prostaglandin (PG) synthesis but not in peripheral tissue while Ibuprofen inhibit prostaglandin (PG) synthesis in peripheral tissue so in this study Paracetamol and Ibuprofen combination used for analgesic, anti-pyretic and anti-inflammatory action simultaneously. The aim of this study was to formulate effervescent tablet with sufficient mechanical integrity and to achieve faster disintegration in the water. Effervescent tablets are uncoated tablets that generally contain acid substances and carbonates or bicarbonates and which react rapidly in the presence of water by releasing carbon dioxide. They are intended to be dissolved or dispersed in water before use. Effervescent compositions in the form of tablets are comprising a therapeutic agent, granulating agent, and an effervescent system which dissolve rapidly in water to yield an effervescent solution containing a completely dissolved therapeutic agent and a process for their preparation. In this study different ratio of Citric acid and Sodium bicarbonate was used, superdisintegrant like SSG and cross-providone was used, compared to cross-providone SSG decreases the Solution time of tablet. Granules prepared by Wet granulation technique and from the result it was found that the Particle size 355-500 µm of granules show good Solution time and Hardness property.

KEYWORDS

Effervescent tablet, COX-1, COX-2, Paracetamol, Ibuprofen.

INTRODUCTION

The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus onset of action is prolong. This can be overcome by administrating the drug in liquid from but, many APIs have limited level of stability in liquid form. So, Effervescent tablets acts as an alternative dosage form. The tablet is added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The tablet is quickly broken apart by internal liberation of CO_2 in water due to interaction between Tartaric acid and Citric acid with alkali metal carbonates or bicarbonates in presence of water.[1]

Effervescent granules are usually prepared from a combination of Citric acid and Tartaric acid rather than from a single acid because the use of either acid alone causes difficulties. When Tartaric acid is the sole acid, the resulting granules readily crumble and lack mechanical strength. Citric acid alone results in a sticky mixture which is difficult to granulate during the manufacturing process.

Effervescent salts include the following ingredients, which actually produce the effervescence, Sodium bicarbonate, Citric acid and Tartaric acid. When added to water the acid

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and base react to liberate carbon dioxide, resulting in Effervescence. It should be noted that any acid-base combination which results in the liberation of carbon dioxide could be used in place of this combination as long as the ingredients are suitable for pharmaceutical use.The reaction between Citric acid and Sodium bicarbonate and Tartaric acid and Sodium bicarbonate, which results in liberation of carbon dioxide, may be shown as follows:[2,3]

$H_3C_6H_5O_7.H_2O + 3\ NaHCO_3 \rightarrow Na_3C_6H_5O_7 + 4\ H_2O + 3\ CO_2$

Citric acid Sodium bicarbonate Sodium citrate Water Carbon dioxide

$H_2C_4H_4O_6 + 2\ NaHCO_3 \rightarrow Na_2C_4H_4O_6 + 2\ H_2O + 2CO_2$

Tartaric acid Sodium bicarbonate Sodium tartarate Water Carbon dioxide

It should be noted that it requires 3 molecules of Sodium bicarbonate to neutralize 1 molecule of Citric acid and 2 molecule of Sodium bicarbonate to neutralize 1 molecule of Tartaric acid. The proportion of acids may be varied. Usually it is desired that ratio of Citric acid to Tartaric acid equals 1:2 so that the desired ratio of the ingredients can be calculated as follows,

Citric acid: Tartaric acid: Sodium bicarbonate=1:2:3.44(by weight)[4,5]

MATERIALS AND METHODS

Paracetmol and Ibuprofen were obtained from Acron Pharmaceutical Pvt. Ltd.(Ahmedabad, India). Spray dried lactose was obtained from Flumost pharmaceuticals (USA). Other ingredients used were of analytical grade.

DRUG - EXCIPIENTS COMPATIBILITY STUDY

Drug-Excipients Compatibility Study by FT-IR

Fourier-transform infrared **(**FT-IR) spectra were obtained using an FT-IR spectrometer. The Zaltoprofen and Excipients were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.[6,7]

Drug-Excipients Compatibility Study by DSC

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The samples (drug and excipients) were heated in sealed aluminum pans under nitrogen flow (30 ml/min) at a scanning rate of 5°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.[8,9]

PREPARATION OF CORE TABLETS

First method[10,11,12]

Wet Granulation: The Wet granulation process performed into three steps

A) Dry Mixing & Granulation

B) Lubrication of Granules

C) Compression of Lubricated Granules

A) Dry Mixing & Granulation

Acid granulation

In first step Weight the Citric acid, Tartaric acid were blended and passed through Sieve No.40#. In second step binding agent pvp-k-30 dissolved in IPA.

The above Organic Solvent was mixed with Acid portions i.e. Citric acid & Tartaric acid. The obtained wet mass passed through sieve no.20# & kept in tray dried at 60^0C for 1 hr.

Base granulation

In Base granulation firstly the Sodium bicarbonate, Sodium carbonate were blended and passed through sieve no.40#In the second step the Binding agent pvp-k-30 was dissolved in Organic solvent i.e. IPA. The above organic solvent was mixed with Base portions i.e. Sodium bicarbonate & Sodium carbonate. The

obtained wet mass passed through sieve no.20# & kept in tray dried at 60^0c for 1 hr.

B) Lubrication of acid and base granules

After drying at Room Temperature of both granules i.e. Acid granules and Base granules were mixed.After mixing of both granules the Paracetamol, Ibuprofen, flavour and Lubricating agent like Sodium benzoate added to the granules and well mixed.

C) Compression of Lubricated Granules

The Lubricated granules were compressed into tablet by using rotary tablet punching machine. (15mm punch)

Second method[18]

Drug (Paracetamol and Ibuprofen), Sodium bicarbonate and Potassium carbonate were blended & passed through sieve no. 40#, granules prepared by using binding agent (8 ml Water and 12 ml Ethanol) & dry at 60^oC for 1 hr. Citric acid, Sodium bicarbonate, Magnesium carbonate, spray dried lactose, SSG, PVP-K-30 and Sodium benzoate were blended and pass through sieve no. 40#, granules prepared by using binding agent (Ethanol) & dry at 60^oC for 30 min. Both granules mix and dry at 60^oC for 15 min. Granules were compressed into tablet by using Single rotary tablet punching machine. (15 mm punch)

EVALUATION PARAMETER

FTIR study

Fourier-transform infrared **(**FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The samples (Zaltoprofen and Excipients) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample:KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

DSC study

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The samples (drug and excipients) were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.

POWDER FLOW PROPERTY

Angle of Repose[13,14]

The angle of repose of the mixture of the drug and excipients was determined by fixed funnel method. The values are used in the following equation to get the angle of repose.

$$\tan \theta = h/r$$

Where, h, r and θ are the height, radius and angle of repose of the powder pile.

Table 1: Relation of Angle of Repose with Powder Flow

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
40 >	Very Poor

Bulk Density and Tapped Density[15]

Accurately weighed of the sample was transferred to the measuring cylinder of bulk density apparatus and noted the volume as bulk volume. The apparatus was adjusted for 100 tapping and noted the final volume as tapped volume.

Bulk density = mass of powder (w) / bulk volume (Vb)

Tapped density= mass of powder (w) / tapped volume (V_{100})

Table 2: Composition of Batches F1-F9 by using Different Binding Agent

Ingredients	**F1***	**F2***	**F3***	**F4***	**F5***	**F6***	**F7***	**F8***	**F9***
Ibuprofen	200	200	200	200	200	200	200	200	200
Paracetamol	325	325	325	325	325	325	325	325	325
Sodium bicarbonate	500	625	750	500	625	750	500	625	750
Citric acid(anhydrous)	250	250	250	250	250	250	250	250	250
Spray dried lactose	20	20	20	20	20	20	20	20	20
Magnesium carbonate	40	40	40	40	40	40	40	40	40
SSG	40	40	40	40	40	40	40	40	40
Sodium benzoate	20	20	20	20	20	20	-	-	-
Mannitol	2%	2%	2%	-	-	-	-	-	-
Ethanol	-	-	-	2%	2%	2%	-	-	-
PEG-6000	-	-	-	-	-	-	2%	2%	2%

*All values are expressed in mg/tablet

Table 3: Composition of Batches F10-F17

Ingredients	**F10***	**F11***	**F12***	**F13***	**F14***	**F15***	**F16***	**F17***
Ibuprofen	200	200	200	200	200	200	200	200
Paracetamol	325	325	325	325	325	325	325	325
Sodium bicarbonate	400	525	650	400	525	650	700	850
Citric acid(anhydrous)	250	250	250	250	250	250	400	400
Potassium carbonate	100	100	100	100	100	100	100	150
Spray dried lactose	20	20	20	20	20	20	20	20
Magnesium carbonate	40	40	40	40	40	40	40	40
SSG	40	40	40	40	40	40	20	20
Cross-providone	-	-	-	-	-	-	-	-
Sodium benzoate	20	20	20	20	20	20	20	20
Pvp-k-30	-	-	-	-	-	-	2%	2%
Pvp-k-30**& Ethanol$^{\#}$	2%	2%	2%	-	-	-	-	-
Pvp-k-30**& Methanol$^{\#}$	-	-	-	2%	2%	2%	-	-
Ethanol+Water**& Ethanol$^{\#}$	-	-	-	-	-	-	2%	2%

*All values are expressed in mg/tablet, **Acid portion, $^{\#}$Base portion

Compressibility Index[16,17]

The Carr's index of the powder was determined by using formula:

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Where, TBD is the total bulk density and LBD is the loose bulk density.

Table 4: Relation of Carr's Index and Hausner's Ratio with Powder Flow

Carr's Index	Flow Characteristics	Hausner's Ratio
< 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Extremely Poor	>1.60

Hausner's Ratio

The Hausner's ratio and Carr's index aremeasures of the flow properties ofpowders. A Hausner's ratio of <1.25indicates a powder that is free flowingwhereas >1.25 indicates poor flow ability.

Hausner's ratio = tapped density / Bulk density

EVALUATION OF THE CORE TABLET

Weight Variation Test

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

Content Uniformity[18,19]

Tablets were crushed in mortal and sufficient amount of ethanol was added to dissolve properly. Then appropriate dilution was done and analyzed by the use of UV Spectrometer at 340 nm.

Hardness

The hardness of the core tablets and coated tables were measured using the Pfizer hardness tester. Six tablets from each formulation were randomly selected and used. The average hardness and the standard deviation were calculated. It is expressed in Kg/cm^2.

Thickness

Thickness of the core tablets and coated tablets were measured by using screw gauge. Ten tablets from each formulation were randomly selected and used. Thickness is expressed in millimeters.

Friability test[20]

Twenty tablets were weight and placed in the Electrolab friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were de-dusted and weight. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

$$\text{Friability}(\%) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} * 100$$

Solution time[21,22]

Time required for 2 tablets to dissolve in 180ml of water at 17.5 ± 2.5°C.

pH of the solution test[23,24]

The pH of solution can measured by pH meter, pH of solution prepared by putting tablets into water was affected by storage condition due to liberation of CO_2.

Water content[25,26]

Titration method used to determine the water content. In contrast to drying method, this is a specific method if no side reactions occur only water will be determined. While using drying method some problem occurs like apart from water, other volatile components of the sample and decomposition products are also determined. Titration method is rapid (few

minutes), can be validated & therefore fully documented. With the Karlfischer (KF) titration both free and bound water can be determined e.g. surface water as crystals or the water content inside them. The method works over a wide concentration range from ppm upto 100% and supplies reproducible and correct result.

Drug content

- Formation of two simultaneous equations were:

Set of two simultaneous equations were:

Cx = (A2 ay1 - A1 ay2)/ (ax2 ay1 - ax1 ay2) and

Cy = (A1 ax2 - A2ax1)/ (ax2 ay1 - ax1 ay2), Where

A1 and A2 are the absorbance of sample solutions at 221.8 nm and 242.2 nm respectively.

Cx and Cy are concentration of Ibuprofen and Paracetamol in mg/mL in sample solution.

By substituting the values of A1 and A2 the values of Cx and Cy can be calculated by solving the two equations simultaneously. Here, ax1 and ax2 are the absorptivity coefficient of Ibuprofen at 221.8 nm and 242.2 nm respectively; ay1 and ay2 are the absorptivity coefficient of Paracetamol at 221.8 nm and 242.2 nm respectively.[27,28]

- Estimation of Paracetamol and Ibuprofen in Tablet:

Mix content of 20 Tablets and calculate the average content weight of one tablet. Take average weight of one tablet and make up the volume of filtrate with Phosphate buffer solution 7.2 pH. Filter this solution i.e. it contains 325mg/100ml of Paracetamol and 200mg/100ml of Ibuprofen, this solution was appropriately diluted to get approximate concentration of 10µg/ml. The absorbance of sample solution was measured at 221.8 nm and 242.2 nm against blank. The content of Paracetamol and Ibuprofen in tablet was calculated using two framed simultaneous equations.[29,30]

RESULT AND DISCUSSION

Interpretation of FTIR spectra

Compatibility studies were performed using FTIR spectrophotometer. The characteristic absorption peaks of pure drug and mixture with other excipientswere obtained at different wave numbers.

The peaks obtained in the spectra of pure drug correlates with the peaks of drug with other excipients. It does not show any major changes in peaks which indicate no well-defined interaction in drug and excipients spectrum. This indicates that the drug is compatible with the formulation components. The spectrum for pure drug and excipients are shown in figure 1 to 4 and interpretations of spectrum are reported in table no.5.

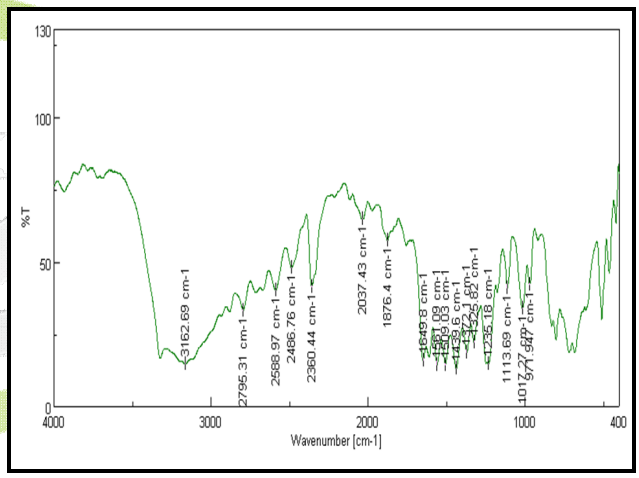

Figure 1: FT-IR Spectrum of Paracetamol

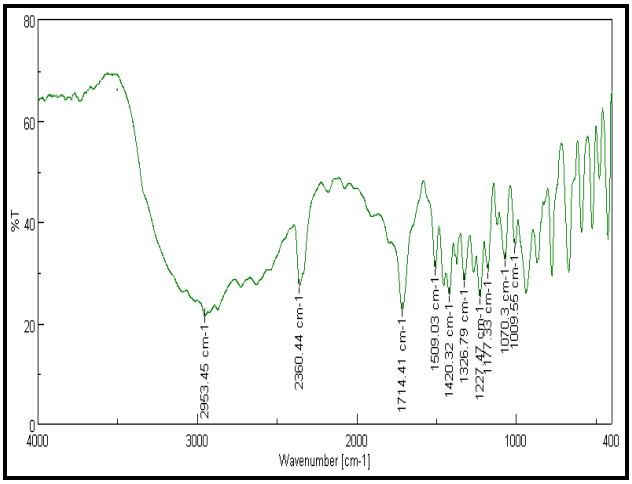

Figure 2: FT-IR Spectrum of Ibuprofen

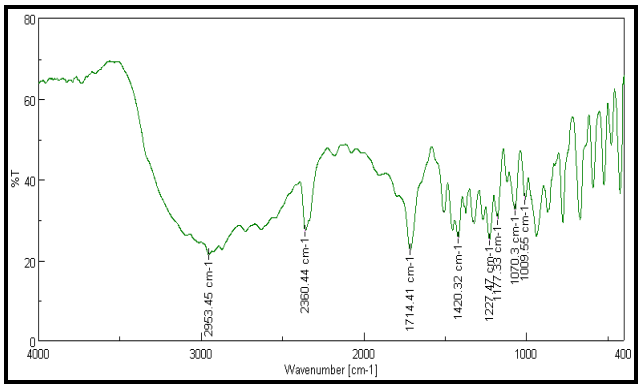

Figure 3: FT-IR Spectra of Paracetamol and Ibuprofen Mixture

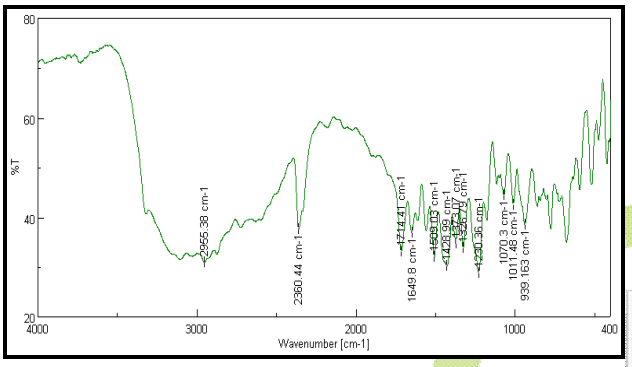

Figure 4: FT-IR Spectra of Paracetamol and Ibuprofen with all Formulation Excipients

Table 5: Interpretation of FT-IR Spectra[21,22]

Group	Wave number (cm^{-1})	
	Paracetamol + Ibuprofen	**Physical mixture**
CH_3 asymmetrical stretching	2953.45	2955.38
O-H…O stretching combination	2360.44	2360.44
C=O stretching	1714.41	1714.41
Amide II band	1509.03	1509.03
CH-CO deformation	1420.32	1428.99
OH in plane deformation	1326.79	1326.79
C….C stretching	1227.47	1230.36
C-N-H group	1070.3	1070.3
Para-disubstituted aromatic ring	1009.55	1011.48

Drug-Excipients Compatibility Study by DSC:

The DSC thermograms of pure drug and with other excipients are depicted in Figure 6.13. Here, pure drug has the melting point at 174 ºC&80^{o}C for Paracetamol and Ibuprofen. Mixture has the melting point at 187 ºC and 85 ^{o}C. No change in the endotherm peak of the drug was observed in the mixture of drug with other excipients. From this, it was inferred that there was no interaction between the drug and excipients.[23,24]

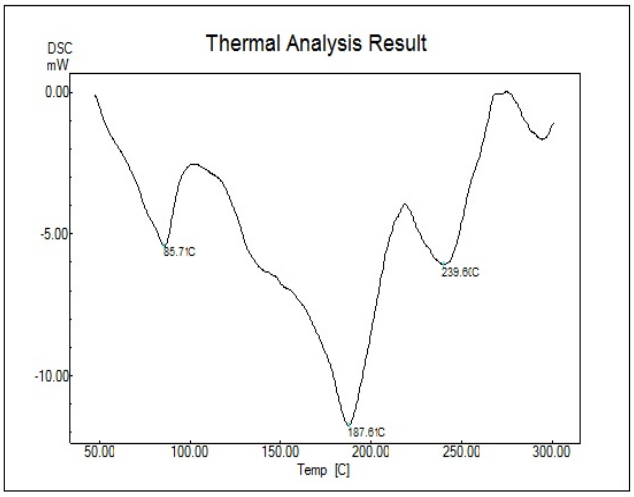

Figure 5: Overlay DSC Thermogram of Pure Paracetamol, Pure Ibuprofen and Physical mixture

Angle of Repose(θ)

The values obtained for angle of repose all (F1-F17) formulations are tabulated in Table 6. All formulation has value in the range of 25.37 to 39.17.This indicates good flow property of the powder blends.

Density

a) Loose bulk Density(LBD)

The values obtained for loose bulk density of (F1-F17) formulations are given in Table 6. The maximum value of LBD was found to be 0.66 and minimum value was found to be 0.50 which indicates good flow property. LBD value of all (F1-F17) formulations ranges between 0.50-0.66.

b) Tapped density

The values obtained for tapped bulk density of all (F1-F17) formulations are in Table 6. TBD value of all (F1-F17) formulations ranges between 0.59-0.79.

Hausner's Ratio

The values obtained for Hausner's ratio for all (F1-F17) formulations are in Table. Hausner's ratio value of all (F1-F17) formulations ranges between 1.12 - 1.26 indicating that the powder blends have good flow property.

Carr's compressibility index

The values obtained for compressibility index for all (F1-F17) formulations are tabulated in Table. Compressibility index of all formulations (F1-F17) was found between 10.81% - 20.77% indicating that the powder blends have good flow property.

Table 6: Evaluation of Powder blend (Batches F1-F17)

Formulations	Angle of repose (θ)	Loose bulk density (LBD)	Tapped bulk density (TBD)	Hausner's Ratio	Carr's Compressibility Index (%)
F1	25.67	0.62	0.70	1.12	11.42
F2	27.06	0.64	0.72	1.13	11.11
F3	36.88	0.60	0.74	1.23	18.91
F4	29.74	0.54	0.62	1.15	12.90
F5	32.23	0.52	0.60	1.15	13.33
F6	29.82	0.55	0.63	1.14	12.69
F7	39.17	0.58	0.72	1.24	19.44
F8	39.53	0.61	0.77	1.26	20.77
F9	38.71	0.63	0.78	1.24	19.23
F10	26.82	0.61	0.69	1.13	11.59
F11	25.57	0.63	0.71	1.13	11.27
F12	28.31	0.58	0.66	1.14	12.12
F13	29.14	0.52	0.60	1.16	13.33
F14	26.87	0.55	0.62	1.13	11.30
F15	31.28	0.53	0.65	1.22	18.47
F16	25.37	0.62	0.70	1.13	11.42
F17	29.81	0.54	0.63	1.17	14.28

Table 7: Evaluation of Tablet (Batches F1-F9)

Formulations	Hardness (kg/cm^2)	Solution time(second)	Friability (%)	Content uniformity(%)	pH of solution
F1	3.5	175	0.71	103*&105#	6.32
F2	4.0	155	0.60	91*&93#	6.11
F3	3.5	142	0.62	91*&97#	6.27
F4	3.0	117	0.85	94*&101#	6.35
F5	2.5	115	0.90	102*&92#	6.12
F6	2.0	117	0.80	99*&107#	6.93
F7	2.5	132	Fail	91*&97#	5.33
F8	2.5	135	Fail	104*&92#	5.47
F9	2.0	128	Fail	94*&101#	5.40

*Paracetamol, #Ibuprofen

Table 9: Evaluation of Tablet (Batches F10-F17)

Formulations	Hardness (kg/cm^2)	Solution time (second)	Friability (%)	Content uniformity (%)	pH of solution	Water Content (%)
F10	3.1	130	0.80	98*&93#	7.00	1.4
F11	3.5	125	0.75	97*&98#	6.95	1
F12	3.2	127	0.81	97*&100#	7.10	1.8
F13	3.5	215	0.73	100*&107#	6.80	-
F14	4.0	187	0.65	104*&92#	7.05	-
F15	3.2	174	0.72	92*&92#	7.10	-
F16	4.5	133	0.30	98*&98#	7.18	1
F17	5.0	128	0.34	99*&97#	7.15	1

*Paracetamol, #Ibuprofen

CONCLUSION

a) In present work we are used different acids and bases in different concentration from that we conclude 1:2.5 ratio was excellent for this formulation.

b) The total nine placebo tablets were prepared and evaluated for hardness, disintegration time, weight variation and solubility. All the formulation shows hardness and weight variation with in limit but the combination of citric acid (20.00%), sodium bicarbonate(42.5%), potassium carbonate(5.0%), magnesium carbonate(5.0%) for thefinal formulation, and the binding agent PVP-K-30(2%) and sodium benzoate (1%).because these ingredients shows the good effervescent reaction and has no problem in capping and sticking like other formulation.

c) These formulations evaluated for hardness, friability, and weight variation, solution time etc. Formulation having acid base ratio 1:2 solution time found 125 to 135 second, ratio 1:2.5 solution time found 115 to 125 second and ratio 1:3 solution time found 105 to 115 second, ratio 1:3 shows good solution time but they hardness was found to be 2 to 3kg/cm2, while ratio 1:2.5 having harness 4 to 5kg/cm2 so acid base ratio 1:2.5 having good Solution time, Hardness and other parameters.

d) The effervescent tablets of Paracetamol and Ibuprofen can be formulated for quick analgesic, anti-pyretic action and anti-inflammatory action by effervescence reaction using citric acid (20%), sodium bicarbonate (42.5%) and magnesium carbonate (5.0%), potassium carbonate (5.0%), pvp-k-30 (2%) gives the better effervescence. The Ethanol used as the binding agent. Sodium benzoate (1%) used as lubricating agent.

e) Water content can be measured by Karl Fischer titration method. Its values reveal that content of moisture in tablet.

f) The effervescent tablets were prepared by wet granulation by using different binding agent like pvp-k-30, mannitol, ethanol, peg-6000 (also act as lubricant).

g) The prepared tablets were evaluated for content uniformity and physical parameters, while using peg-6000 and mannitol as binding agent the solution time was low compared to pvp-k-30 and ethanol.

h) When acid granulation and base granulation performed separately hardness problem occurs and Ibuprofen not soluble in a glass of water at the time of taking medicines. To overcome Ibuprofen solubility problem base part granulate with drug i.e Paracetamol and Ibuprofen using binding agent ethanol and water, remaining part like acid, base, lubricant granulate with ethanol in this part pvp-k-30(2%) added in dry form, developing formula by above method having good evaluations parameters.

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