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PREPARATION AND EVALUATION OF EFFERVESCENT TABLETS OF 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. Ibuprofen inhibits prostaglandin (PG) synthesis in peripheral tissue. The aim of this study was to formulate effervescent tablet with sufficient mechanical integrity and to achieve faster disintegration in the water. In preformulation study compatibility evaluation was performed which implies that drug acids bases and other excipient are compalible with each other different acid and base were based in combination to prepare tablet. Tablets were also prepared using different binding agent and evaluated for hardness, friability, solution time and pH of solution, effervescences. Tablet prepared using higher ratio of NaHCO3 and citric acid and pvp-K30 2% as binder show short solution time, higher pH and also has good hardness.

Keywords: Effervescent tablet, COX-1, COX-2, 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 powders used as Saline cathartics were available in the eighteenth century and were subsequently listed in the official compendia as compound Effervescent powders. There were commonly known as 'Seidlitz powders'. Effervescent mixtures have been moderately popular over the years since along with the medicinal value of the particular preparations, they offered the public a unique dosage form that was interesting to prepare. In addition, they provided a pleasant taste due to Carbonation which helped to mask the objectionable taste of the drugs.[2] The choice of ingredients for effervescent granules depends both upon the requirement of the manufacturing process and the necessity of making a preparation which dissolves in water. The required ingredients are at least one acid and at least one base. The base must release carbon dioxide upon reaction with the acid. Example of such Acids include Tartaric acid and Citric acid, Example of bases include Sodium carbonate, Potassium bicarbonate, and Sodium bicarbonate. 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.[3]

Effervescent tablet have major advantage that the drug product is already in solution at the time it is consumed. Thus the absorption is faster and more complete than with conventional tablet. Faster absorption means faster onset of action. Effervescent drug are delivered to the stomach at a pH that is just right for absorption. Many medication travel slowly through the GIT or have absorption that is hampered by food or other drug. Effervescent tablet dissolve fully in a buffered solution. Reduced localized contact in the upper GIT leads to less irritation and greater tolerability. Buffering also prevent gastric acids from interacting with drug themselves, which can be a major cause of stomach. [4,5]

There is a problem to provide a dosage form which includes the NSAIDs together with excipients useful to formulate the tablet into the dosage form and also excipients useful to ensure rapid disintegration, but not to provide a tablet that is too large for patient consumption or cannot be produced according to standard large scale manufacturing process. [6]

Several clinical studies have also indicated that the start and the intensity of the analgesic effects correlate to the plasma-ibuprofen-concentration. Ibuprofen level results in an increased analgesic effect. Another study has shown that soluble Ibuprofen starts to relieve pain earlier than Ibuprofen tablets. Ibuprofen is an organic acid having a poor solubility. Only just at a pH-value 7 does the acid form a salt whereby the solubility is increased significantly (pK-value of ibuprofen acid- 4.5). Because of the immense circulation of Ibuprofen it would be substantially helpful if Ibuprofen acid could be made to dissolve more rapidly and less pH-dependently by the skillful choice of adjuvant and without complicating the preparation of the drugs. [7, 8, 9, 10, 11]

MATERIALS AND METHODS

Materials

Ibuprofen was received as a gift sample from Acron Pharmaceuticals Limited, Ahmedabad, Gujarat, India. Other excipients like citric acid, tartric acid, spray dried lactose, PVP-K-30, dicalcium phosphate, mannitol were also received as gift sample form Acron Pharmaceuticals Limited, Ahmedabad, Gujarat, India.

Experimental Methods

Particle size distribution

The size and size distribution of the granules produced was determined by agitation for 10 min with a sieve shaker fitted with a progression of standard sieves. From the weight retained on each sieve, a cumulative weight under size graph was plotted from which the median diameter was determined.

Angle of Repose

This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. 10 gm of drug were allowed to flow by funnel from 4 cm of height from the base. The height of pile and diameter of base was measured and calculate the angle of repose by following formula:

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

$$\theta = \tan^{-1}\frac{h}{r}$$

Preparation of Tablets

Effervescent tablets of ibuprofen were prepared by two different methods.

Method-I: Method-I was based on dry granulation and had two different stages of granulation known as acid granulation and base granulation, respectively. **Stage-I:** 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. **Stage II:** 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.

After drying at Room Temperature of both granules i.e. Acid granules and Base granules were mixed. After mixing of both granules the Ibuprofen, flavor and Lubricating agent like Sodium benzoate added to the granules and well mixed. The Lubricated granules were compressed into tablet by using rotary tablet punching machine. (15mm punch)

Method-II: Drug (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 oxide, 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)

Formulation composition of effervescent tablet of ibuprofen was shown in Table 1.

Table 1: Formulation Composition of Effervescent Tablets of Ibuprofen

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ibuprofen	200	200	200	200	200	200	200	200	200	200
Sodium bicarbonate	400	525	650	400	525	650	700	850	700	850
Citric acid(anhydrous)	250	250	250	250	250	250	400	400	400	400
Potassium carbonate	100	100	100	100	100	100	100	150	100	150

Spray dried lactose	20	20	20	20	20	20	20	20	20	20
Magnesium oxide	40	40	40	40	40	40	40	40	40	40
SSG	40	40	40	40	40	40	20	20	-	-
Cross-providone	-	-	-	-	-	-	-	-	20	20
Sodium benzoate	20	20	20	20	20	20	20	20	20	20
Pvp-k-30(dry)	-	-	-	-	-	-	2%	2%	2%	2%
Pvp-k-30(acid portion)& Ethanol(base portion)	2%	2%	2%	-	-	-	-	-	-	-
Pvp-k-30(acid portion)& Methanol(base portion)	-	-	-	2%	2%	2%	-	-	-	-
Ethanol+ Water(acid portion)& Ethanol(base portion)	-	-	-	-	-	-	2%	2%	2%	2%

EVALUATION OF EFFERVESCENT TABLETS

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.

Hardness test

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.

Friability test

Twenty tablets were weight and placed in the friability test apparatus 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%.

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

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.

Solution time

Time required for 2 tablets to dissolve in 180ml of water at Room Temperature.

pH of the solution test

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

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.

Content Uniformity

Twenty tablets were randomly selected from each batch and individually selected. The average weight and standard deviation of 20 tablets was analyzed. Tablets contain not less than 90% and not more than 110% of labeled amount of Ibuprofen.

RESULTS AND DISCUSSION

Evaluation of granules

Particle size Distribution

The different particle size of prepared granules of all formulations (F1-F10) is tabulated in Table 2.

Angle of Repose (θ)

The values obtained for angle of repose all (F1-F10) formulations are tabulated in Table. All formulation has value in the range of 25.37 to 39.17.This indicates good flow property of the powder blends. Results of angle of repose and other powder characteristics were shown in Table 3.

Tablet 2: Particle size analysis of granules

Formulation	Particle size (µm)				
	710 – 1000 (µm)	500 – 710 (µm)	355 – 500 (µm)	180 – 355 (µm)	≥ 180 (µm)
F1	6.32 %	2.63%	36.84%	39.37%	14.84%
F2	4.26%	2.88%	39.85%	36.54%	16.47%
F3	5.66%	3.45%	37.52%	36.84%	16.53%
F4	6.74%	3.46%	43.30%	31.83%	14.67%
F5	4.84%	4.54%	51.53%	28.64%	13.51%
F6	5.37%	2.45%	56.82%	33.64%	15.36%
F7	6.75%	3.61%	52.25%	26.45%	10.94%
F8	6.57%	4.65%	53.15%	24.36%	11.27%
F9	6.47%	2.92%	48.04%	28.93%	13.64%
F10	6.82%	3.36%	43.02%	32.68%	14.12%

Table 3: Evaluation of the Powder blend

Formulations	Angle of repose (θ)	Bulk density (BD)	Tapped density (TD)	Hausner's Ratio	Compressibility Index (%)
F1	26.82	0.61	0.69	1.13	11.59
F2	25.57	0.63	0.71	1.13	11.27
F3	28.31	0.58	0.66	1.14	12.12
F4	29.14	0.52	0.60	1.16	13.33
F5	26.87	0.55	0.62	1.13	11.30
F6	31.28	0.53	0.65	1.22	18.47
F7	25.37	0.62	0.70	1.13	11.42

F8	29.81	0.54	0.63	1.17	14.28
F9	28.68	0.57	0.66	1.15	13.67
F10	27.93	0.54	0.62	1.15	12.90

Evaluation of the Tablet

Prepared tablets were evaluated for different tablet evaluation parameters like solution time, hardness, friability, content uniformity, pH of the solution, and water content. Results of effervescent tablet evaluation were depicted in Table 4.

Table 4: Evaluation of Effervescent Tablet

Formulations	Hardness (kg/cm^2)	Solution time (second)	Friability (%)	Content uniformity (%)	pH of solution	Water Content (%)
F1	3.1	130	0.80	105.12	7.00	-
F2	3.5	132	0.75	109.65	6.95	-
F3	3.2	129	0.81	96.95	7.10	-
F4	3.5	300	0.73	101.85	6.80	-
F5	4.0	310	0.65	105.35	7.05	-
F6	3.2	280	0.72	102.21	7.10	-
F7	4.5	133	0.30	97.35	7.18	1
F8	5.0	120	0.34	99.99	7.15	1
F9	3.5	135	0.45	99.98	7.05	1.8
F10	4.0	140	0.53	98.96	7.13	1.6

The maximum thickness of the formulation was found to be 5.8 mm. The minimum thickness of the formulation was found to be 5.2 mm. The solution time of all the formulated (F1-F10) tablets was found to be 120 to 310 second. The pH of the solution of all the formulated (F1-F10) tablets was found to be 6.95 to 7.18. The maximum water content of the formulation F9 was found to be 1.8%. The minimum water content of the formulation F7 and F8 was found to be 1%. According to B.P. water content not more than 1%. The hardness of the tablet was found to be 2.0 to 5.0 kg/cm^2.

The maximum friability of the formulation was found to be 0.98%. The minimum friability of the formulation was found to be 0.30%. The % friability was less than 1% in all the formulations (F1-F10) ensuring that the tablets were mechanically stable. The drug content of all the formulation (F1-F10) was found to be 96.95% to 109.65%. According to I.P. limit of content for tablets contain not less than 90% and not more than 110% of labeled amount of Ibuprofen.

According to predetermine criteria for optimized formulation among all 10 formulations formulation F8 was selected as optimized formulation for effervescent tablets, because it had lower friability, higher drug content, lower solution time.

Stability Study

The selected Formulation F8 were evaluated for stability studies which were stored at room temperature and tested after 15 days and after 30 days, and were analyzed for their solution time and drug content at that interval. The residual drug contents of formulations were found to be within the permissible limits and the results of 15 days and 30 days duration were shown in the Table 5.

Table 5: Stability Parameters of Formulation F8, at Room Temperature

Parameter	Initial	After 15 days	After 30 days
Solution time (second)	120	120	119
Drug content (%)	99.99	99.96	99.95

CONCLUSION

The effervescent tablet can be prepared using different acids such as citric acid, tartaric acid in different concentration and various lubricants and binding agents also used. There are 25 formulations that contain the citric acid, tartaric acid, sodium bicarbonate, Potassium carbonate and magnesium carbonate. These 25 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/cm^2, while ratio 1:2.5 having harness 4 to 5kg/cm^2 so acid base ratio 1:2.5 having good Solution time, Hardness and other parameters. From the above summary it

was concluded that, the effervescent tablets of 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.

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