



Design and Characterization of Aceclofenac Mouth Dissolving Tablets by Effervescent Formulation Approach

Ravikumar¹, Sachin R Patil¹, MB Patil¹, Mahesh S Paschapur¹ and Mahalaxmi R²

¹Dept of Pharmaceutics, KLES College of Pharmacy, Ankola, Karnataka, India

²Dept of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal, Karnataka, India

Abstract

Aceclofenac is a novel non-steroidal anti-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties and is widely used in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Though aceclofenac is well absorbed after oral dosing, there is a first pass metabolism leading to a reduced bioavailability of the drug (40-50%). Therefore, the present investigation was concerned to develop Mouth dissolving tablets of aceclofenac by effervescent formulation approach to provide patient friendly dosage form. The effervescent excipient system not only aids rapid disintegration of tablets in the oral cavity but also masks the slight bitter taste of medicament. Sodium bicarbonate, heat treated Sodium bicarbonate, tartaric acid, sodium glycine carbonate and citric acid were used as effervescent agents and their ratio in the formulation was optimized. The study revealed that 10:8 ratio of heat treated Sodium bicarbonate and citric acid (F3) in the aceclofenac Mouth dissolving tablets gave a soothing fizz, excellent mouth feel, good palatability and quick dissolution profile. The optimized formulation (F3) was found to be stable during the stability studies conducted as per ICH guidelines, as it showed no significant changes ($P < 0.05$) in the physicochemical properties, disintegration time and *in vitro* drug release.

Key Words: mouth dissolving tablets, effervescence, aceclofenac, *in vitro* dissolution.

Introduction

The oral route of administration is considered as the most widely accepted route. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients in compliance particularly in case of pediatric and geriatric patients [1]. Thus, a new delivery system known as oral fast dissolving/disintegrating (FDSD)/melt-in-mouth tablets gaining importance. These oral

dosage forms dissolve rapidly in saliva and can be swallowed without the need of drinking water[2]. Elimination of bitterness is an important criterion in product formulation of mouth dissolving tablets[3]. Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Recently, more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients[4-5]. Many patients, elderly people and person with dysphagia find it difficult to swallow the tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy. Addition of effervescent system in the formulation is one of the approach by which mouth dissolving tablets can be prepared[6-9]. The major advantages with effervescent formulation approach that it is a well established, easy to implement and mask the bitter taste of drug[10]. The effervescent system is generally composed of a dry acid and dry base which when react facilitate a mild effervescent reaction when the tablets contacts saliva. The effervescent reaction accelerates the disintegration of tablet through the release of carbon dioxide, water and salt. Due to evolution of carbon dioxide the bitter taste of drug is also masked and a pleasant mouth feel is felt[11].

Soluble effervescent tablets get quickly dissolved when put in water to give a sparkling solution with good taste which can be easily consumed by patients with dysphagia. Citric acid (CA) is very hygroscopic and it poses challenge to formulators hence, it was selected. Also market preparations like ENO and DISPIRIN contain CA and hence they were selected so that comparison of humidity resistance of our formulation can be made. Tartaric acid (TA) is comparatively less hygroscopic so it was used in the present work.

Aceclofenac, (2-[2-[2-(2,6-dichlorophenyl)aminophenyl]acetyl]oxyacetic acid), a nonsteroidal antiinflammatory drug (NSAID) has been indicated for various painful indications[12] and proved as effective as other NSAIDs with lower indications of gastro-intestinal adverse effects and thus, resulted in a greater compliance with treatment[13]. Aceclofenac is practically insoluble. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. Clear aceclofenac-loaded soft capsules have been prepared to accelerate the absorption[14]. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion)[15]. The dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution.

The aim of present work was to develop mouth dissolving tablets of aceclofenac by effervescent formulation approach. The objective behind the study was to optimize the ration of effervescent agents that would produce pleasing mouth feel and good palatability.

Materials and Methods

Aceclofenac was obtained as gift sample from (Aristo Pharmaceuticals Ltd, Mumbai, India), Microcrystalline cellulose PH101 (Zydus Research centre, Ahmedbad), Croscarmellose sodium (DMV International, Mumbai.), Citric acid, tartaric acid, sodium bicarbonate (SD Fine chemicals, Mumbai). All other chemicals, reagents and solvents are of either analytical or Pharmacopoeial grade.

Characterization of Drug and Excipients

Fourier Transform Infra Red Spectroscopy (FTIR)

FTIR spectra of pure aceclofenac and physical mixture of drug and excipients were recorded on Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC. Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400- 4000 cm^{-1} at spectral resolution of 2cm^{-2} and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

Differential Scanning Calorimetry (DSC)

Thermal properties of the pure drug and the physical mixture of drug and excipients were analyzed by Shimadzu DSC-60, Shimadzu Limited Japan. The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350 $^{\circ}\text{C}$ at a heating rate of 10 $^{\circ}\text{C}/\text{min}$, using nitrogen as blanket gas.

Preparation of aceclofenac granules

The sodium bicarbonate and citric acid were used in the ratio of 4:3, 8:6, 10:8, 10:10, 12:6 and 25:20 in these formulations. All the ingredients were accurately weighed and sifted through sieve no.44. Sodium bicarbonate and citric acid were preheated at a temperature of 80 $^{\circ}\text{C}$ to make them anhydrous and then added to other ingredients. Required quantity for each formulation and all the ingredients were coground in a mortar and pestle. Absolute alcohol was used as binder to prepare the granules. The wet mass was screened through sieve no. 60 and dried. The dried granules were sieved through sieve no. 40 and subjected for evaluation of granules.

Evaluation of Granule Blend

Prior to compression into tablets, dried granules blend were evaluated for following precompression properties which includes;

1. Angle of repose

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h , was obtained. Diameter of heap, D , was measured. The angle of repose, Θ , was calculated by formula

$$\tan \Theta = h / r$$
$$\Theta = \tan^{-1} (h / r)$$

Where, Θ is the angle of repose, h is the height in cm and r is the radius.

2. Bulk Density

Apparent bulk density was determined by pouring pre- sieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by

$$D_b = M / V_0$$

Where, M is the mass of powder and V_0 is the Bulk volume of the powder.

3. Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by

$$D_t = M / V_t$$

Where, M is the mass of powder and V_t is the tapped volume of the powder.

4. Powder flow properties

The flow properties were determined by

i) Carr's Index (I)

It is expressed in percentage and is expressed by

$$I = D_t - D_b / D_t$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

ii) Hausner ratio

It is expressed in percentage and is expressed by

$$H = D_t / D_b$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Compression of tablet

After evaluation of granule blend were then mixed with talc, magnesium stearate, silicon dioxide and pineapple flavor for five minutes. The mixed blend of granules were compressed using a single punch tablet punching machine at a fixed compression force to produce flat faced tablets weighing 300 mg each with a diameter of 10 mm. A minimum of 100 tablets were prepared for each batch (Table1).

Table 1: Formulation and evaluation of batches of aceclofenac effervescent tablet

Ingredients* (mg)	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Aceclofenac	100	100	100	100	100	100	100	100	100	100
Avicel pH 101	30	30	30	30	30	30	30	30	30	30
Aspartame	9	9	9	9	9	9	9	9	9	9
Citric acid	9	18	24	30	18	60	--	--	24	--
Sodium bicarbonate	12	24	--	30	36	75	--	--	30	--
Sodium glycine carbonate	--	--	--	--	--	--	30	30	--	--
Tartaric acid	--	--	--	--	--	--	24	30	--	24
Heat treated sodium bicarbonate	--	--	30	--	--	--	--	--	--	30

Cross carmellose sodium	15	15	15	15	15	15	15	15	15	15
Pineapple flavor	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
talc	6	6	6	6	6	6	6	6	6	6
Silicon dioxide	3	3	3	3	3	3	3	3	3	3
mannitol	108.5	87.5	75.5	69.5	75.5	0	75.5	69.5	75.5	75.5
Total weight of tablet (mg)	300	300	300	300	300	300	300	300	300	300

*All batches contained absolute alcohol as a binder/granulating agent

Evaluation of tablets

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually.

Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

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

In vitro Disintegration test

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (mesh no. 10) was immersed in water bath at $37 \pm 2^{\circ}\text{C}$. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the Pharmacopoeial standards, dispersible tablets must disintegrate within 3 min when examined by the disintegration test for tablets.

In vitro dispersion test

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an oro-dispersible tablet. *In vitro* dispersion time was measured by dropping a tablet in a

measuring cylinder containing ml of simulated salivary fluid of pH 6.8. Five tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 5ml of Methanol and made up to volume with phosphate buffer pH 6.8. The sample was mixed thoroughly and filtered through a 0.45 μ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λ_{max} of 273 nm using phosphate buffer pH 6.8 as blank.

Wetting time and water absorption ratio

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 6 ml of simulated saliva pH 6.8. A tablet having amaranth powder on the upper surface was placed on the filter paper. Time required to develop red color on the upper surface of tablet was recorded as wetting time. Three tablets from each formulation were randomly selected and the average wetting time was noted. Wetting time corresponds to the time taken for the tablet to disintegrate when placed gently on the tissue paper in a Petri dish. This method will duplicate the *in-vivo* disintegration as the tablet is motionless on the tongue. Less is the wetting time indicates more porous the tablets.

***In vivo* disintegration time**

Six healthy human volunteers were selected and their written consent was obtained. Each volunteer randomly took one tablet and kept on the tongue. The time taken for complete disintegration of the tablet on the tongue was noted. It is expressed in seconds. After the test, mouth was washed with distilled water. Three trials were performed with 2 days interval, between trials.

Mouth feel

The same human volunteers participated in taste evaluation test, were asked to give their opinion about the feeling of smoothness or grittiness of the dispersion soon after the tablet got disintegrated.

Taste evaluation

Taste evaluation was done by a panel of six volunteers using time intensity method. One tablet was held in mouth for 10 s bitterness levels were recorded instantly and then at the end of 10 s, 30 s, 1 min, and 2 min, bitterness levels are again noted and recorded.

Measurement of tablet porosity

The porosity of the tablet was calculated from bulk and true tablet volume. It was calculated from the measured tablet diameter, thickness, true density of powder using the following equation $E = 100 (1 - V_t/V_b)$, Where V_t and V_b are the true and the bulk volume. The diameter and thickness of the tablet were measured with a micrometer. The true density of the powder was determined using a helium pycnometer (AccuPyc 1330, Micrometitics Instrument Inc., Norcross, GA).

pH determination

Tablets from various batches were put in a beaker containing 30 ml of distilled water and temperature was maintained at 25°C. The pH was measured after complete disintegration of

the tablet using Mettler pH measuring apparatus. The consistent measurement of solution pH is a sign of good distribution of raw materials within the tablet.

Thermal stressing of packaged tablets

The prepared tablets packed in an aluminum foil from various batches (5 each) were placed in a 75°C convection oven for 3 hour. It was then allowed to cool to room temperature. Once at room temperature, each of the aluminum foil were then peeled under controlled temperature and humidity conditions and assessed for the degree of tablet mottling. Because the tablets were colored, any effervescent reactions that occurred could easily be seen as darker spots or mottling on the tablet.

Mottling detection of stressed tablets

Tablets were given a rating from 0-4 (least to most) for the degree of tablet mottling. Packaged tablets of each formula that had not been thermally stressed acted as controls. These tablets were given a mottling score of zero. All the stressed tablets were graded in a blinded fashion to minimize the variability and bias in the evaluation.

Moisture uptake and effervescent stability studies

Moisture determinations for various excipients were carried out by their respective U.S.P. and/or N.F. methods (US Pharmacopoeia 27/NF22., 2000). Loss on drying for compendial methods was performed in a hot air convection oven. Tablets were placed in desiccators containing saturated aqueous solutions of sodium chloride solution (75%RH). Samples were also kept at 50°C in capped glass bottles in a stability chamber. At predetermined time intervals, samples were withdrawn. The water uptake was measured gravimetrically (n=3).

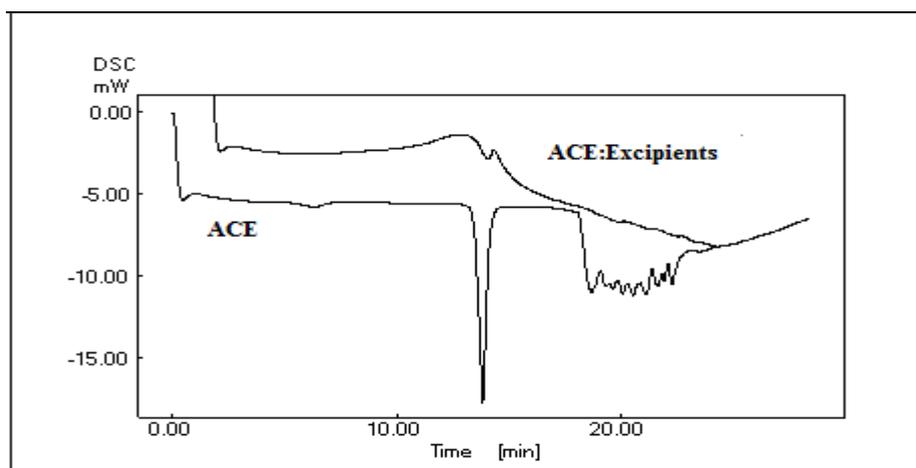
Results and Discussion

Patience convenience and compliance oriented research has resulted in bringing out many safer and newer drug delivery systems. Fast dissolving tablet is one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self administration even without water or chewing. Many drugs with these needs were attempted for formulating as fast dissolving tablets. In the present study one such nonsteroidal antiinflammatory drug aceclofenac mainly indicated in cases of osteoarthritis, rheumatoid arthritis, acute lumbago, and dental pain condition was tried formulating as fast dissolving tablet. Formulated tablets resulted with advantages like ease of administration, suitable for pediatric and geriatric patients with no water intake especially during journey. Quick dissolving, high drug load with better taste and minimum mouth feel are other advantages.

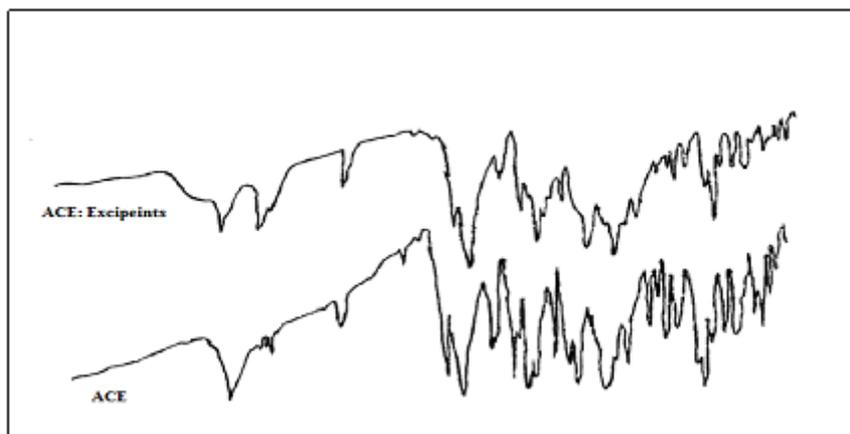
Drug Excipient Compatibility Study

Differential Scanning Calorimetry (DSC)

DSC is useful in the investigation of solid-state interactions. The DSC analysis of pure aceclofenac showed a sharp endothermic peak at 156.54°C corresponding to its melting point. The thermograms were generated for pure drug and drug excipient mixtures. The DSC analysis of physical mixture of the drug and excipients revealed negligible change in the melting point of aceclofenac in the presence of other excipients (152.91°C for the mixture of aceclofenac and citric acid). The thermograms are shown in Fig.1.

Fig1. DSC Thermograms of aceclofenac alone and its physical mixtures**Fourier Transform Infrared (FTIR) Spectroscopy**

The IR spectral analysis of aceclofenac alone showed that, the principle peaks were observed at wave numbers of 3276, 1770 and 3317 cm^{-1} . Confirming the purity of the drug as per the established standards. In the IR spectra of the physical mixture of the aceclofenac and excipients, the major peaks of aceclofenac were 3276, 1770 and 3317 cm^{-1} wave numbers. However no additional peaks were observed in physical mixture of the aceclofenac and excipients. IR spectra are shown in Fig.2.

Fig2: IR Spectrum of aceclofenac alone and its physical mixtures**Precompression parameters of powder blend**

Precompression parameter for the formulations prepared by effervescent technique is shown in Table 2. Bulk density was found to be between 0.52 ± 0.04 to 0.58 ± 0.01 g/cc and tapped density between 0.67 ± 0.02 to 0.763 ± 0.03 g/cc, bulkiness between 1.74 ± 0.04 to 1.89 ± 0.05 . Carr's index between 16.1 ± 0.03 to 25.8 ± 0.04 %, Hausner ratio between 1.22 ± 0.02 to 1.35 ± 0.05 and angle of repose was found to be between 25.0 ± 0.02 to $29.7 \pm 0.02^\circ$, indicating fair to good flow properties.

Table 2: Results of Precompression Properties of aceclofenac granules

Formulation code	Angle of repose(°)*	Bulk density (gm/cm ³ *)	Tapped density (gm/cm ³ *)	Carr's index (%)*	Hausner ratio (H _R)*	Bulkiness (cc/g)*	Granule property
F1	27.5±0.02	0.57±0.02	0.67±0.02	20.8±0.03	1.26±0.04	1.89±0.05	Sticky
F2	25.1±0.03	0.52±0.04	0.68±0.01	16.1±0.03	1.29±0.04	1.75±0.04	Slightly sticky
F3	27.5±0.04	0.57±0.03	0.67±0.01	21.6±0.02	1.30±0.02	1.89±0.04	Non sticky
F4	26.1±0.01	0.58±0.01	0.73±0.01	21.1±0.02	1.32±0.01	1.75±0.04	friable
F5	28.0±0.01	0.57±0.01	0.69±0.01	17.6±0.05	1.24±0.04	1.74±0.02	Non sticky
F6	29.7±0.02	0.55±0.02	0.73±0.02	24.7±0.04	1.22±0.05	1.80±0.04	friable
F7	25.1±0.03	0.56±0.03	0.71±0.02	21.1±0.04	1.27±0.04	1.76±0.04	Non sticky
F8	26.1±0.01	0.53±0.02	0.72±0.02	25.8±0.04	1.35±0.05	1.85±0.04	Non sticky
F9	26.0±0.02	0.55±0.01	0.73±0.03	17.6±0.01	1.24±0.01	1.74±0.04	Non sticky
F10	25.1±0.02	0.56±0.02	0.71±0.03	24.7±0.04	1.22±0.02	1.80±0.01	Non sticky

*All values are expressed as mean ± SD, n=5

Evaluation of post compression parameters of aceclofenac effervescent tablets

The tablets of different formulations (F1 to F10) were evaluated for various parameters viz; thickness, diameter, hardness, friability, percentage weight variation and percentage drug content. All the formulations showed uniform thickness and diameter. In a weight variation test, the Pharmacopoeial limit for the percentage deviation for the tablets of more than 250mg is ± 5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Drug content was found to be uniform among different batches of the tablets, and the percentage of the drug content was more than 97%. The hardness of all the formulation was between 3.8 to 4.2 kg/cm². The percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness and friability (Table 3).

It was found that there is a positive correlation between wetting time, water absorption ratio and disintegration time (*in vivo* and *in vitro*) as shown table 4.

The wetting time of formulation F3 was 28 seconds containing citric acid and heat treated sodium bicarbonate in ration of 8:10, which was lower than other formulations. The percentage of water absorption was between 28.17 to 42.73. The disintegration time of the tablets varied from 30 to 38 seconds. The tablet containing citric acid and heat treated sodium bicarbonate in ration of 8:10, disintegrates faster than tablets prepared with other formulations as shown in Table 4.

Table 3: Results of Post Compression Properties of aceclofenac effervescent Tablets

Formulation code	Diameter (mm)*	Thickness (mm)*	Hardness (kg/cm ²)*	Friability (%)***	Drug content (%)**	Weight variation (mg)**
F1	11.0±0.01	3.0±0.01	4.2±0.1	0.42±0.01	99.45±0.02	299±0.01
F2	10.8±0.01	3.1±0.02	3.8±0.12	0.42±0.02	99.98±0.03	300±0.01
F3	10.7±0.01	3.2±0.02	4.1±0.05	0.44±0.01	101.21±0.02	298±0.01
F4	11.0±0.02	2.8±0.02	3.9±0.09	0.55±0.04	97.56±0.02	297±0.02
F5	11.1±0.02	2.9±0.02	4.0±0.08	0.41±0.03	98.32±0.03	301±0.02
F6	11.2±0.01	3.0±0.01	3.8±0.01	0.61±0.03	98.12±0.04	302±0.02
F7	11.0±0.02	3.0±0.02	4.0±0.02	0.41±0.03	98.35±0.05	300±0.03
F8	11.0±0.02	2.9±0.01	3.8±0.03	0.58±0.05	97.15±0.05	298±0.03
F9	11.1±0.03	3.0±0.02	4.0±0.04	0.45±0.01	99.15±0.02	298±0.03
F10	11.0 ±0.01	2.8±0.03	4.1±0.06	0.31±0.01	100.12±0.03	297±0.03

*All values are expressed as mean ± SE, n=5; **All values are expressed as mean ± SE, n=20; ***All values are expressed as mean ± SE, n=10.

Aceclofenac is insoluble in water and only 45% of the oral dose is absorbed through gastro intestinal tract. The absorption of Aceclofenac is dissolution rate limited. As shown in table 4, the percentage Aceclofenac absorbed from oral cavity ranges from 6-8%. This might be due to the increase in solubility of Aceclofenac at the pH of the saliva. Effect of storage time on porosity could also indirectly measure the initiation of any effervescent reaction. As shown in table 4; maximum porosity value for control batches and more or less similar values for other formulation batches. These values are consistent from 2 and 4 weeks confirmed that maximum effervescent reaction takes place within two weeks. Temperature has less pronounced effect on the stability of the tablets than relative humidity as shown by the I_R values. This shows the strong correlation between humidity and storage condition. The ingredients used in effervescent tablets have very good tableting properties and hence they give tablets with very good appearance. Appearance was judged visually Very good (+++), good (++), fair (+), poor (-), very poor (- -).

Taste evaluation

The healthy human volunteers participated in taste evaluation test, were asked to give their opinion about the feeling of smoothness or grittiness of the dispersion soon after the tablet got disintegrated. Formulation F3 showed smooth and pleasant mouth feeling, which shows excellent taste masking effect of the aspartame and flavors. Thus fulfill the requirements of oro-dispersible tablets.

Table 4: Results of Post Compression Properties of aceclofenac effervescent Tablets

Formulation code	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Porosity (%)**	18.32 ±0.014	22.13 ±0.015	16.18 ±0.015	15.98 ±0.015	15.76 ±0.016	14.95 ±0.016	13.25 ±0.012	20.12 ±0.012	16.21 ±0.012	15.45 ±0.013
Wetting time (sec)**	37.0 ±2.0	38.0 ±3.25	28.0 ±4.25	33.0 ±5.21	35.0 ±2.12	38.0 ±3.12	35.0 ±1.25	40.0 ±3.0	38.0 ±3.0	40.0 ±2.2
Water absorption ratio (sec)**	32.58 ±2.45	36.66 ±4.21	28.17 ±3.20	39.12 ±4.10	42.16 ±3.21	42.73 ±5.21	35.45 ±2.45	38.21 ±3.10	36.65 ±2.15	32.43 ±3.31
In vivo disintegration Time (sec)**	36.0 ±4.12	35.0 ±3.15	30.0 ±5.35	32.0 ±4.65	34.0 ±2.13	38.0 ±5.30	36.0 ±4.20	38.0 ±6.02	34.0 ±2.45	33.0 ±6.10
In vitro disintegration time (sec)**	32.0 ±3.15	28.0 ±2.12	20.0 ±4.32	28.0 ±5.65	30.0 ±2.10	31.0 ±5.12	32.0 ±4.02	33.0 ±5.14	30.0 ±3.41	29.0 ±5.30
Appearance*	++	+	+++	-	+	++	++	+	+	++
Aceclofenac absorbed from buccal cavity (%)**	6.72 ±0.12	7.48 ±0.89	8.43 ±0.68	7.54 ±0.75	8.26 ±0.92	7.49 ±0.75	3.15 ±0.54	5.45 ±0.87	4.32 ±0.74	5.12 ±0.69
pH	9.3	9.2	9.7	9.8	10.2	9.3	8.9	8.5	9.2	9.0

*+++ =best, ++ =good, + =satisfactory, - = worst; **All values are expressed as mean ± SE, n=5.

Sensory evaluation/mouth feel

Sensory study was carried out on disintegration time, mouth feel attributes like grittiness, chalkiness, and overall preference. The study included five subjects. The subjects were asked to record the time for the tablet to completely dissolve in the mouth and give scores for mouth feel attributes and overall liking of the product. Ranking is as follows. 1=best, 2 = good, 3 = satisfactory, 4=worst. Details of the sensory study and preference between various batches were given in Table 5. Although grittiness and chalkiness are similar in all the batches the time to dissolve in the mouth might be the reason between the differences among the overall preferences between various batches. It has shown that although there is a close similarity between the batches but F3 is superior. This might be due to shorter time for dissolution thereby less chalkiness feelings from microcrystalline cellulose.

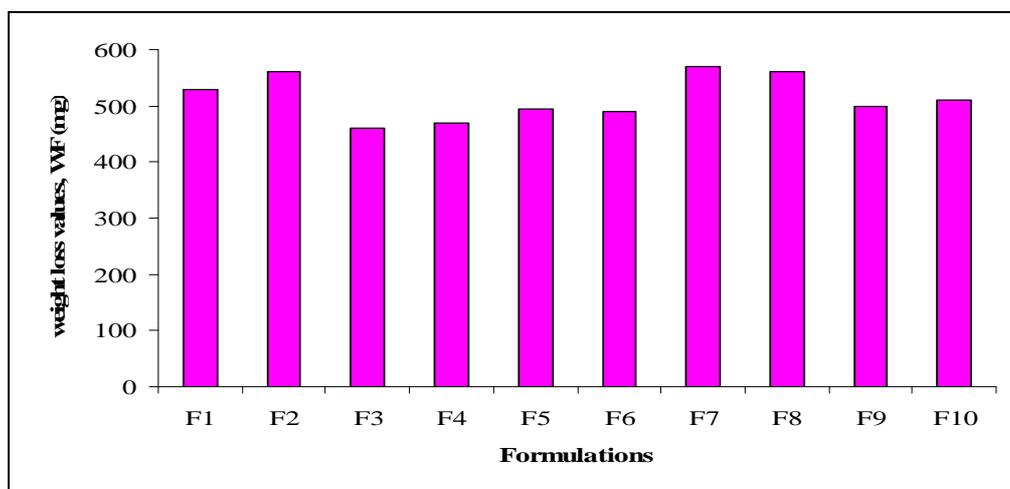
Figure 3 shows the weight of CO₂ loss of batch F2, F7 and F8 was significantly reduced on storage at room temperature and also at 75% RH for 30 days due to premature effervescence. The weight of carbon dioxide lost at any time during the effervescent reaction was given as W_a and final weight loss measured 2 minutes after the reaction was started was designated as W_F. F2, F7 and F8 has shown highest values compared to other acid and base sources combination. Plotting log (W_F - W_a) versus time graph will indicate the three events observed during the effervescent reactions.

Table 5: Sensory study on disintegration time and mouth feel attributes

Parameters	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Time to dissolve (sec)	2	2	1	2	3	2	3	2	2	2
Grittiness	2	2	1	2	2	2	2	3	2	2
Chalkiness	2	2	1	2	3	2	3	2	2	2
Overall preference	2	2	1	2	2	2	2	2	2	2

*1=best, 2=good, 3=satisfactory, 4=worst

They are lag time (wetting period), actual time of the effervescent reactions, latent period in which the effervescent reaction has stopped and carbon dioxide slowly coming out of the solution. From the slope of the first order plot reaction rate constant 'k' can be calculated. Respective reaction rate constant values from various batches are given in Fig 4. It shows maximum values for F2, F7, F8. The index of reactivity I_R , which combines both reaction rate and total carbon dioxide involved (W_F) is the product of both reaction rate constant and final weight loss and respective values are given in Figure 5.

Figure 3: Comparison of carbon dioxide weight loss from various effervescent formulations***In vitro* drug release**

The *in vitro* drug release from tablets containing citric acid and heat treated sodium bicarbonate in ration of 8:10, was above 95% and drug release from tablets s containing citric acid and sodium bicarbonate in ration of 8:10 and was above 65% within 10 minutes. The drug release profiles of all prepared tablets are shown in Figure 6.

The dissolution profiles of marketed tablet and optimized fast dissolving effervescent aceclofenac tablets (F3) were determined in phosphate buffer pH 6.8. The result showed (figure7) that fast dissolving tablets have better dissolution rate than the marketed tablets. So fast dissolving effervescent aceclofenac tablet could increase the bioavailability of aceclofenac.

Figure 4: Average reaction rate constant from various effervescent formulations

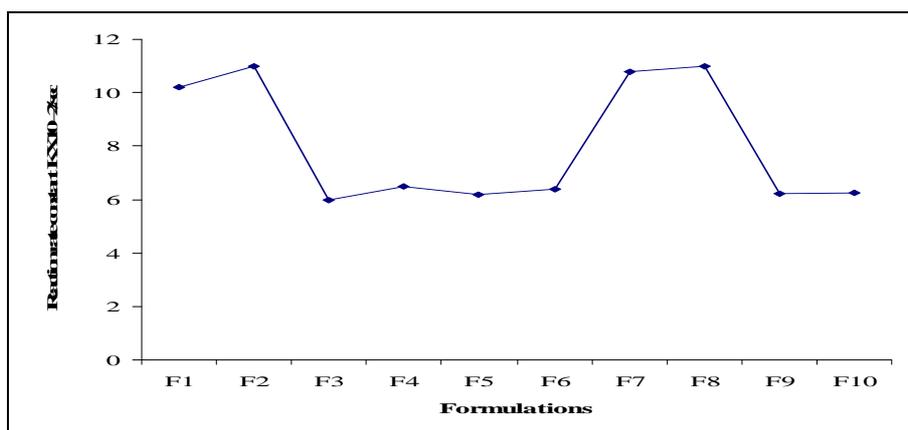


Figure 5: The effect of storage time on the index of reactivity values from various effervescent formulations

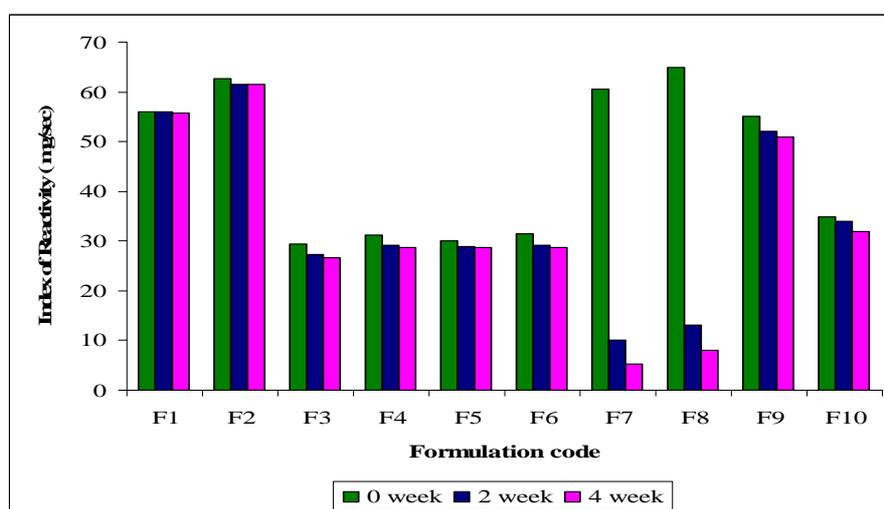


Figure 6: Comparison of *In vitro* release of various effervescent formulations.

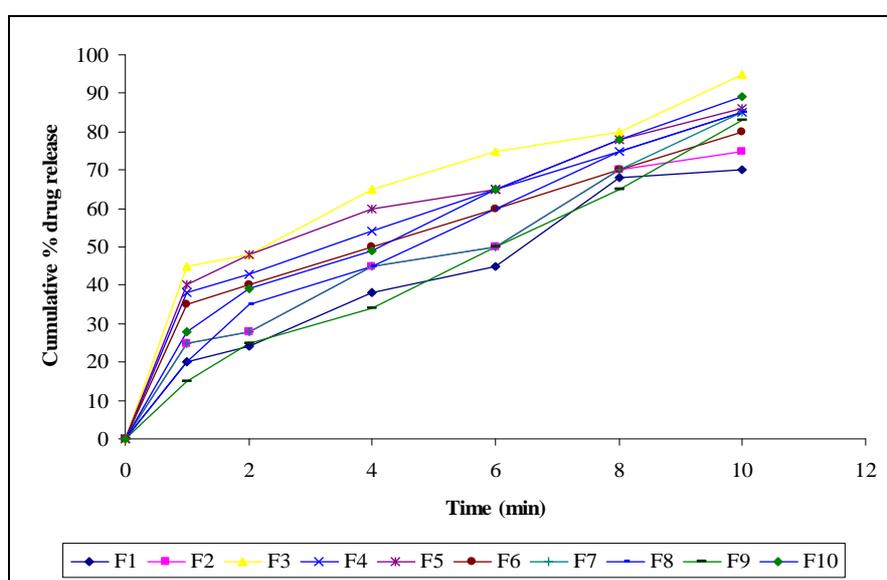


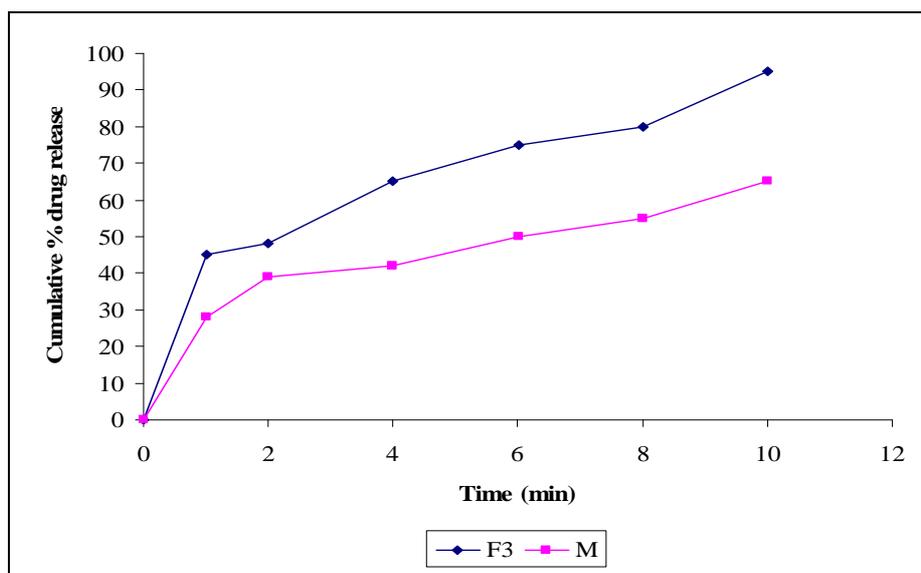
Figure7: Comparison of *In vitro* release of optimized and marketed formulation

Table 6 showed the heat treated base is substantially stable. The reason was obvious as controlled heat treatment ensured formation of a layer of sodium carbonate on the sodium bicarbonate due to partial conversion. The partial conversion ensures surface passivation of the sodium bicarbonate due to formation of a desiccant skin of sodium carbonate which enhanced the moisture proofness of sodium bicarbonate[16]. The surface passivated sodium bicarbonate may also prevent premature effervescence on coming in contact with the moisture. Thus, it was decided to use heat treated base in place of normal sodium bicarbonate to get stable effervescent tablet. Batch F3 showed substantial improvement in the stability of the tablet after using heat treated sodium bicarbonate. Also there was non-significant change in hardness, friability so, it was concluded that use of treated sodium bicarbonate has definitely contributed to the stability of the tablet. Thus, batch F3 (containing heat treated sodium bicarbonate) was the optimized stable effervescent tablet batch. After being stored in high relative humidity, tablets have not shown any significant physical changes in F3 as indicated by smooth surface and lack of swelling. But other batches showed the presence of effervescent reaction as shown by rough, porous and swollen surface. This has been once again proved by the thermal stress study and mottling assessment of stressed tablets. Non uniform distribution of color on the surface indicates the presence of effervescent reaction if any.

Table 6: Comparative % moisture absorption by treated and untreated sodium bicarbonate

Test Parameters	Results	
	Untreated NaHCO ₃	Modified NaHCO ₃
% Moisture absorption	0.6	0.4

Stability study

The formulation for stability studies were selected based on the shorter disintegration time in the oral cavity, wetting time and mouth feel of the final formulation. Based on the above requirements, the formulation coded F3 is selected.

Figure 8: Stability study of optimized formulation (F3)

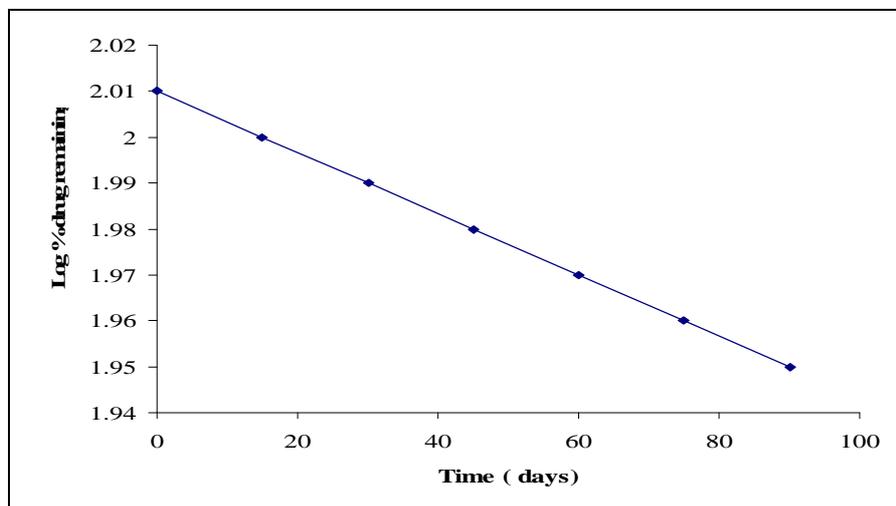
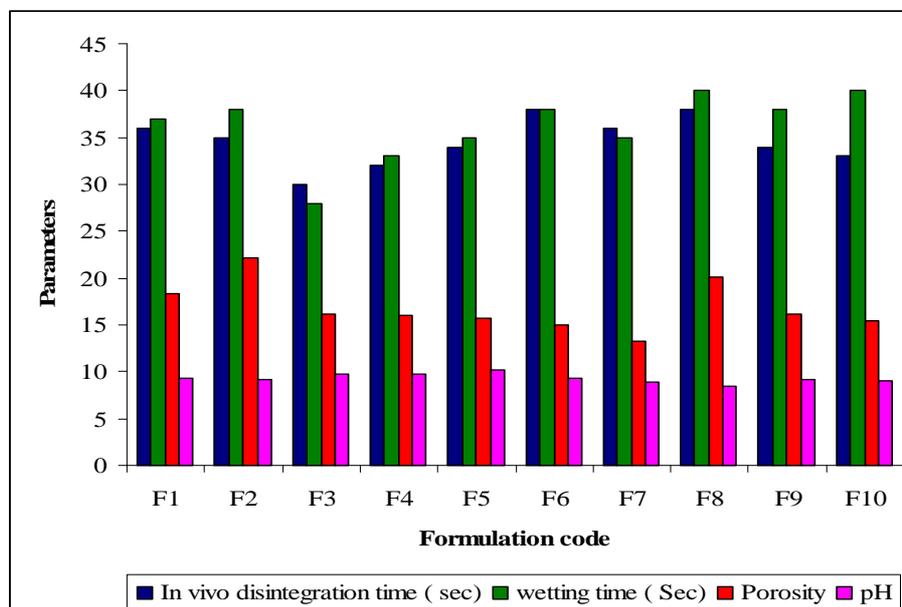


Figure 9: Comparison of pH from different batches along with wetting time, porosity, *in vivo* disintegration time



The optimized formulation F3 were charged on accelerated stability and monitored for appearance, hardness, friability, drug content, *in vitro* dispersion time, *in vivo* disintegration time, wetting time and dissolution profile study at 1,2 and 3 month. The stability study reveals no significant variation in appearance, color, odor, taste, hardness, friability, drug content, *in vitro* dispersion time, *in vivo* disintegration time, wetting time and *in-vitro* dissolution study up to three months stability studies for F3 formulations at

40°C±2°C/75±5%RH. The formulation was stable under accelerated conditions of temperature and humidity. Statistical analysis of the mean cumulative drug release in pH 6.8 phosphate buffer has shown that the differences are nonsignificant ($P \geq 0.05$). Stability profile for the optimized formulations (F3) was shown in figure 8.

Determination of pH from different batches showed consistent values thereby indicates that raw materials are uniformly distributed. pH from different batches was affected by storage condition due to liberation of CO₂. Appearance of tablets was altered and also hardness and friability were affected substantially. The cause of decrease in hardness and increase in friability of tablets was due to liberation of CO₂ which had rendered tablets porous.

Comparison of pH from different batches with porosity, wetting time and *in vivo* disintegration time was compared. There is a positive correlation between pH, wetting time and porosity. Increase in pH showed a slight decrease in wetting time and porosity (figure 9).

Conclusion

Fast dissolving tablets of aceclofenac is successfully prepared by using effervescent technique, Undoubtedly the availability of various technologies and the manifold advantages of fast dissolving tablets will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability, and its popularity in the near future. The stability studies of selected effervescent systems have shown that the described experimental procedure has significantly improved the stability of the effervescent tablets. The index of reactivity has been used as a successful experimental tool for the effervescent tablet reactivity combining both the amount of carbon dioxide generation and reaction rate of the effervescent reaction. The study of the effervescent system showed that the stability of the effervescent tablet was dependent on the tablet formulation, storage conditions, and length of time the tablet was stored. The present formulation using citric acid-heat treated sodium bicarbonate is found to have better reaction properties and reaction stability than does the other batches. Finally sensory study on disintegration time and mouth feel attributes ranked the present formulation based on grittiness, chalkiness and overall preference as best. Fast effervescent tablets (F3) provides an excellent mouth feel and good physical stability since it melts at about 37°C. This dosage form is convenient, economically feasible and needs only a modification of the conventional tableting method.

Acknowledgments

The authors would like to thank Aristo Pharmaceuticals Ltd, Mumbai, India for providing gift sample of aceclofenac. The authors also thank Dr.M.B.Patil, Principal, KLES college of Pharmacy, Ankola, Karnataka, for providing all the facilities and encouragement for the research work.

References

- [1] SV Sastry; JR Nyshdham; JA Fix. *Res Focus Pharma Technol*, **2000**, 3,138-45.
- [2] MR Redkar; SP Gore; PV Devrajan. *Indian J Pharm Sci*, **2002**,64, 291-2.
- [3] B Yunxia; Y Yorinobu; S Hisakozu. *J Pharm Sci*, **1999**, 88, 1004-10.
- [4] SY Bhusan; SP Sambhaji; RP Anant; RM Kakasaheb. *Indian Drugs*, **2000**,37,312-8.
- [5] AR Wadhvani; NB Prabhu; MA Nandkarni; PD Amin. *Indian J Pharm Sci*, **2004**,7,506-7.

- [6] J Michaelson. *US patent*, 4,14, 198, **1983**.
- [7] F Wehling; S Shuehle. *US patent*, 5, 178, 878, **1993**.
- [8] F Wehling; S Shuehle. *US patent*, 5, 503, 846, **1996**.
- [9] SI Pather; RK khankari; JD Eichman; JR Robinson; J Hontz. *US patent*, 6, 200, 604, **2001**.
- [10] W Tritthart ; MA Piskering. *US patent*, 6, 245, 353, **2001**.
- [11] HA Libermann; L Lachmann; JB Schwartz. *Pharmaceutical dosage forms: tablets*, Vol.1, 2nd edn, Marcel Dekker Inc, USA, 285-327.
- [12] B Hinz; D Auge; T Rau; S Rietbrock; K Brune; U Werner. *Biomed Chromatogr*, **2003**,17, 268-75.
- [13] E Legrand. *Exp Opin Pharmacother*, **2004**, 5,1347-57.
- [14] CS Yong; YK Oh; KH Lee; SM Park; YJ Park; YS Gil. *Int J Pharm*, **2005**, 302, 78-83.
- [15] Martin A. *Physical pharmacy*. 4th edn, Philadelphia: Lippincott Williams and Wilkins; **1993**, 324-62.
- [16] Effer – Soda sodium bicarbonate, SPI Pharma technical Bulletin, SPI Pharma group, Europe/middle East/Asia.