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FORMULATATION DEVELOPMENT AND EVALUATION OF EFFERVESCENT TABLET OF PARACETAMOL AND N-ACETYLCYSTEINE.

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ABSTRACT

The main aim of the work is to design and develop stable formulation of effervescent tablets of Paracetamol and N-Acetylcysteine and to evaluate respective formulation. The present work is directed to a new pharmaceutical formulation comprising Paracetamol and N-acetylcysteine in the form of effervescent tablet to be taken orally and offering a considerable advantage over other dosage forms.Paracetamol is an analgesic and anti-pyretic agent. It is clinically used for temporary relief of fever, minor aches, and pains. N-acetylcysteine is a mucolytic agent and also used as Paracetamol poisoning antidote. Market Survey revealed that Paracetamol and N-Acetylcysteine in combination are introduced in market as tablet and syrup dosage form. Due to the high dose and taste problems of Paracetamol and N-acetylcysteine it is difficult to formulate in film coated tablet dosage form or as syrup due to stability issues. So, Effervescent Tablets acts as an alternative dosage form. Effervescent tablets are designed to be dissolved or dispersed in water before administration. Since effervescent tablets are administrated in liquid form; they are easily swallowed so they are preferred over tablets or capsules.

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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[1,2]. Effervescent tablets are designed to be dissolved or dispersed in water before administration. The tablet is promptly broken apart by internal release of CO2 in water and the CO2 reaction is created by an interaction of tartaric acid and citric acid with alkali metal carbonates or bicarbonates in the presence of the water. Effervescent tablets are uncoated tablets that usually consist of acids and bicarbonates or carbonates[3,4]. Some products are useful for pharmaceuticals that damage the stomach or those which are susceptible to stomach pH. In addition, the drugs prescribed commonly in high doses may be used in the form of effervescent tablets. Moreover, since effervescent tablets are administrated in liquid form; they are easily swallowed so they are preferred over tablets or capsules with a difficult consumption for some patients[5,6]. On the other hand, one dose of effervescent tablet is often dissolved in 3-4 ounces of water. Being previously dissolved in a buffer solution, effervescent products do not get in direct contact with the gastrointestinal tract. They can thus be tolerated in stomach and intestine well due to reduced gastrointestinal irritation[6].

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. Due to liberation in CO_2 gas, the dissolution of API in water as well as taste masking effect is enhanced. The advantages of effervescent tablets compared with other oral dosage forms includes an opportunity for formulator to improve taste, a more gentle action on patient's stomach and marketing aspects.

Effervescent tablets are uncoated tablets that generally contain acid or acid salts (Citric, tartaric, malic or any other suitable acid or acid anhydride) and carbonates or bicarbonates (Sodium, potassium or any other suitable alkali metal carbonate or hydrogen carbonate), which react rapidly in the presence of water by releasing carbon dioxide. Due to liberation in CO_2 gas, the dissolution of API in water as well as taste masking effect is enhanced[7,8].

The reaction between Citric acid and Sodium bicarbonate and Tartaric acid and Sodium bicarbonate, which results in liberation of carbon dioxide shown as follows:

$C_6H_8O_7.H_2O + 3NaHCO_3\ (aq) \rightarrow Na_3C_6H_5O_7 + 4H_2O + 3CO_2\ (g) \uparrow$

Citric acid + Sodium bicarbonate → Sodium citrate + Water + Carbon dioxide

$C_4H_6O_6 + 2\ NaHCO_3 \rightarrow Na_2C_4H_4O_6 + 2H_2O + 2CO_2\ (g) \uparrow$

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)[1,,3,4,9,10].

MATERIALS AND METHODS

Materials

Paracetamol and N-Acetylcysteine was supplied by Farmson Pharmaceutical Pvt. Ltd., Vadodara and Ningo Haide Amino Acid, China, respectively. Citric acid,povidone, sodium bicarbonate, sodium carbonate, simethicone, malic acid, sucralose was supplied by SciTech Specialities Pvt. Ltd., Sinner.India. Orange flavour and aniseed flavour was supplied by lux flavour, Chennai.India..

Determination of λ max of Paracetamol:

In 10 ml volumetric flask appropriately 1 ml of aliquot of the stock solution taken and diluted up to the mark with the 0.1 N NaOH solution. Resulting solution was scanned between 400 nm to 800 nm on UV/Visible spectrophotometer (Shimadzu 1800). d. Preparation of calibration curve of Paracetamol in 0.1 N NaOH: Series of dilutions such as 2, 4, 6, 8, 10µg/ml were prepared from stock solution. Absorbance was measured at λmax using double beam UV spectrophotometer.

Determination of λ max of NAC:

In 10 ml volumetric flask appropriately 1 ml of aliquot of the stock solution taken and diluted up to the mark with the 0.1 N NaOH solution. Resulting solution was scanned between 400 nm to 800 nm on UV/Visible spectrophotometer (Shimadzu 1800).

Preparation of calibration curve of Alendronate sodium in water:

Series of dilutions such as 2, 4, 6, 8, 10µg/ml were prepared from stock solution. Absorbance was measured at λmax using double beam UV spectrophotometer.

Differential Scanning Calorimetry (DSC):

The DSC was performed on a DSC-60, Shimadzu differential scanning calorimeter with thermal analyzer. Accurately weighed sample (about 2 mg of sample) was placed in sealed aluminum pan, before heating under nitrogen flow (20 ml/min) at a scanning rate of 10^0 C per min from 0 to 200^0 C. An empty aluminum pan was used as reference.

Drug-excipient compatibility study:

The primary objective of this study was to check the compatibility of proposed excipients for tablet formulation. Instead of compatibility, identification of stable storage condition for the tablet.

Infra Red (FTIR) spectroscopy:

The 1:1 proportion of drug: excipients were taken in petriplates. Two sets of each excipient were prepared. One set were kept in the sealed vials for final analysis at 50ºC/80 % RH for 1 month. Another set was analyzed at the time of sets preparation for visual inspection, IR spectral analysis. The IR spectrum of powder mass was recorded using IR spectrophotometer (Carry 630, Agilent). Sample was placed in the sample holder and the spectrum was scanned over a frequency range 4000– 400 cm-1. [39, 40]

Differential Scanning Calorimetry (DSC):

The drug and excipients mixture without moisture was prepared in petriplates. The DSC analysis was performed on a DSC-60, Shimadzu differential scanning calorimeter with thermal analyzer. Accurately weighed sample (about 2 mg of sample) was placed in sealed aluminum pan, before heating under nitrogen flow (20 ml/min) at a scanning rate of 10^0 C per min from 0 to 300^0 C. An empty aluminum pan was used as reference. [26, 39,41]

Evaluation of precompression blend:

Determination of Angle of repose, Car's index and Hausner's ratio were used to characterize flow properties of the powder or blend. The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies, otherwise, high dose variations will occur.

Angle of repose

Angle of repose for blend of each formulation was determined by fixed funnel method. The funnel is secured with its tip with height h, above a plane of paper kept on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reaches the tip of funnel. Angle of repose was determined by substituting the values of the base radius „r‟ and height of the pile „h‟ in the given eq. given below, [42]

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

Where, θ= angle of repose, h = height of heap,r = radius of base of heap circle

Bulk density.

Approximately 50 gm of test sample was accurately weighed and sifted through 18# sieve and transferred in a 100 ml graduated cylinder. The level was observed without compacting and noted as apparent volume (V0). [5, 42] The bulk density was calculated by the formula as given below:

$$\text{Bulk density} = M / V0$$

Where, M=Mass of powder taken. V0= Apparent untapped volume.

Tapped density:

Approximately 50 gm of test sample was accurately weighed and sifted through 18# sieve and transferred in 100 mL graduated cylinder. The cylinder was placed on the tapped density tester and was mechanically tapped, allowing it to drop under its own weight that provides a fixed drop from 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and the tapped volume (V1) was measured to the nearest graduated units. The tapping was repeated for additional 750 times and the tapped volume (V2) nearest to graduated units was noted. [5, 42] The tapped density was calculated by the formula as given below:

$$\text{Tapped density} = M / V2$$

Where,
M= Weight of powder, V2= Tapped volume (after 750 taps).

Carr's Index:

It is used to evaluate flowability of powder by comparing the bulk density and tapped density of a powder. The percentage compressibility of a powder is direct measure of the potential of powder arch or bridge strength is calculated according to the equation given below:[5,23,42]

Hausner's ratio:

Hausner found that the ratio tapped density/bulk density was related to inter particle friction as such, could be used to predict powder flow properties. He showed that the powder with low inter particle friction had ratio of approximately 1.2, where as more cohesive less free flowing powders have Hausner‟s ratio greater than 1.6. Hausner‟s ratio less than 1.25 indicate good flow. [23]

Manufacturing process development:

The manufacturing process of Paracetamol & NAC Effervescent Tablet developed as follows.

A. Laboratory Batches: Laboratory Scale batches of 1 kg were taken. All the equipments (Octagonal Blender, Rapid mixer granulator, Fluidize Bed Dryer, Multi mill, Shifter, Tablet Compression machine) used for Laboratory Scale batches were of small capacity and suitable to carry out the laboratory scale operation.

Description of manufacturing process:

Paracetamol & NAC Effervescent Tablets (Paracetamol 500 mg and NAC 600 mg)

Sifting:

Sift the materials as per the sequence and specified mesh sieves. Check residue if any, from each material for appearance and quantity. The integrity of the sieve is checked before and after sieving. Paracetamol & NAC were passed through 100 #, Citric Acid and Sodium bicarbonate is passed through 60 #.

Blending:

Blend 'A': In octagonal blender accurately weighed Paracetamol and NAC were added with citric acid and blended for 10 min at 15 RPM.

Blend 'B': In octagonal blender accurately weighed sodium bicarbonate, sodium carbonate, sucrose, sucralose, PVP K30, malic acid and flavours were added and blended for 10 min at 20 RPM.

Granulation:

Preparation of Binder Solution: 12.5 gm of PVP K30 was dissolved in 100 ml of distilled water. Granulation (Blend 'A'): In rapid mixer granulator (RGM) blend „A" was added then dissolve PVP K30 in sufficient amount of water & pour on blend „A" and run for 4 min.

Drying:

Blend 'A': Dry blend 'A' in FBD (Fluidize Bed Dryer) at inlet temp 550 C and outlet temp 650 C and product bed temp 400 C – 450 C for 15 min.

After Drying IPQC test of Appearance and Loss on drying was performed.

IN-PROCESS CONTROL

1. Check the appearance: White color, uniformly dried granules
2. Loss on drying : Not more than 0.4 %

Final Blending:

In octagonal blender accurately weighed Blend „A" and Blend „B" were added and mixed for 15 min at 24 RPM then accurately weighed amount of sodium benzoate was added to octagonal blender and again blended for 5 min at 24 RPM.

After Blending IPQC test of Appearance and Loss on drying

IN-PROCESS CONTROL

1. Check the appearance : White color granules
2. Loss on drying : Not more than 0.3 %

Compression:

Add blend in Accura D4, 12 station tablet Compression machine and compressed by using 25 mm flat punch.

Packing:

The compressed tablets are packed into 40µ, 2 Ply Aluminum foil having Total GSM 138. Each strip contains 4 Tablets.

Evaluation of effervescent tablet formulation:

Prepared tablets were subjected to evaluation of different properties including drug content uniformity, weight variation, tablet hardness, friability, tablet dimensions, disintegration time test and statistical analysis. Drug content analysis of paracetamol and NAC was also performed.

Sensory Evaluation of taste by Panel testing (human subjects):

The panel testing is a psychophysical rating of the gustatory stimuli. In vivo taste evaluation carried out on a trained taste panel of healthy volunteers with organoleptic sense, with their prior consent. Before beginning the evaluation, the taste ability of volunteers is measured by four base tastes (salt, sweet, sour, bitter) by 20 ml of 0.2% sodium chloride, 2% sucrose, 0.07% citric acid, and 0.07% caffeine in water respectively. The sample of effervescent solution is subject to sensory evaluation by a panel of nine members with respect to bitter taste. The members of a panel are asked for taste evaluation (by retaining the formulation in mouth for10-30s) and later on to gargle for complete removal of taste sense of previous samples and then after 15 minutes the next sample is given for taste evaluation. The evaluation is performed and the panel is asked to grade the formulation as per six levels.

Level 5: Strongly bitter taste is sensed.
Level 4: Moderately bitter taste is sensed
Level 3: Slightly bitter taste is sensed.
Level 2: Acceptable.
Level 1: Palatable
Level 0: No bitter taste is sensed.

Stability studies: (ICH guidelines, 2005) [46]

In any rationale design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During stability studies the product is exposed to accelerated conditions of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature for short period or time. The optimized formulations sealed in aluminum packaging and kept in the humidity chamber maintained at 25ºC/60% RH, 30ºC/65% RH and 40ºC/75% RH conditions for three months. The samples of 20 tablets were randomly withdrawn on initial stage, after one month and three months. These samples were analyzed for the physical appearance, hardness, solution time, pH of solution and drug content. The averages of all results were shown in result table 9.14 and 9.15Resp

RESULT AND DISCUSSION.

Drug-excipient compatibility study:

Infra Red (FTIR) spectroscopy:

FTIR spectrum of Paracetamol: NAC (1:1) and pre-compressible blend:-

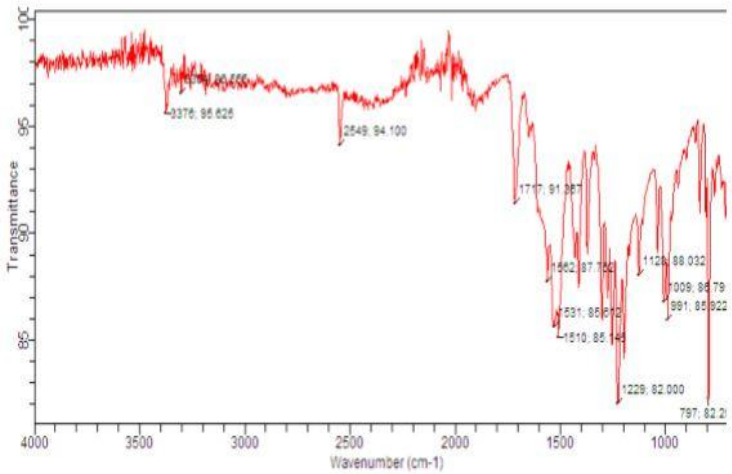

Fig. 3.1 IR spectra of paracetamol : NAC (1:1) mixture.

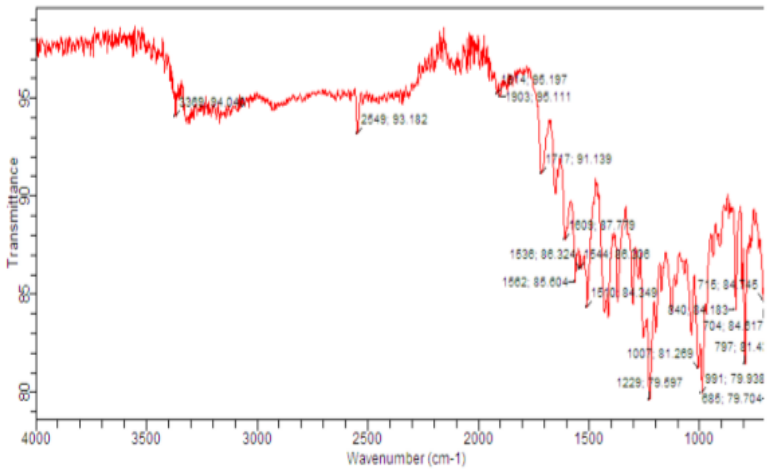

Fig. 3.2 IR spectra of paracetamol, NAC and Excipients.

Differential scanning calorimetry Analysis

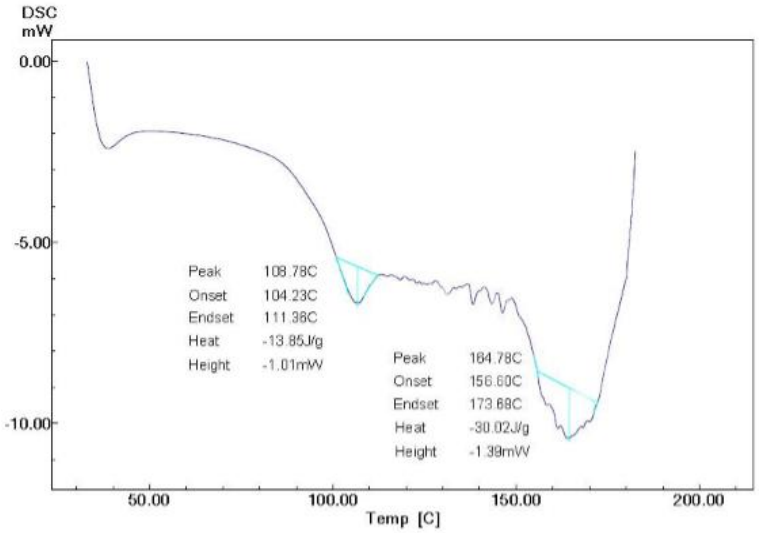

Fig. 3.3 DSC Thermogram of Paracetamol, NAC and Excipient Mixture.

Evaluation of Precompression Blend:
Precompression evaluation of Paracetamol and NAC Effervescent Tablets.

Formulation	Angleof repose (^{0})	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio
F1	25.56 ± 0.0015	0.849±0.001	0.903±0.001	5.98±0.01	1.063±0.002
F2	25.64±0.01	0.852±0.001	0.906±0.002	5.96±0.03	1.063±0.003
F3	25.76±0.0057	0.854±0.002	0.909±0.002	6.5±0.04	1.064±0.001
F4	25.84±0.01	0.857±0.002	0.914±0.001	6.23±0.04	1.066±0.001
F5	25.78±0.015	0.859±0.001	0.917±0.003	6.32±0.05	1.067±0.003
F6	26.08±0.0057	0.859±0.003	0.911±0.003	5.7±0.12	1.06±0.002
F7	25.70±0.0057	0.854±0.002	0.909±0.001	6.05±0.04	1.064±0.002
F8	25.74±0.01	0.857±0.002	0.914±0.002	6.23±0.10	1.066±0.001
F9	25.83±0.015	0.857±0.001	0.911±0.003	5.92±0.02	1.063±0.001

All values are expressed as mean ± SD (n=3).

Evaluation of Effervescent Tablets

Formulations	Thickness (mm)	Hardness (kg/cm^2)	Weight Variation
F1	5.81 ±0.005	4.5±0.057	4.025±0.014
F2	5.80±0.01	5.0±0.1	4.105±0.014
F3	5.79±0.015	4.0±0.152	4.035±0.01
F4	5.82±0.01	5.2±0.152	4.030±0.006
F5	5.81±0.021	4.7±0.2	4.035±0.013
F6	5.78±0.015	5.0±0.1	4.015±0.011
F7	5.80±0.02	6.5±0.057	4.027±0.005
F8	5.80±0.01	6.0±0.1	4.027±0.005
F9	5.80±0.01	6.2±0.152	4.005±0.013

All values are expressed as mean ± SD (n=3).

Evaluation of Effervescent Tablets

Formulations	Solution time (sec.)	pH of solution	Drug Content(%)	
			Paracetamol	NAC
F1	160.33±0.079	6.43±0.053	102.11 ±0.080	100.45±0.028
F2	130.50±0.079	6.15±0.053	103.49±0.069	101.22±0.026
F3	90.30±0.091	5.82±0.025	101.20±0.060	100.34±0.026
F4	110.00±0.096	5.74±0.045	99.17±0.083	102.94±0.035
F5	80.00±0.115	5.70±0.015	99.17±0.083	100.34±0.035
F6	98.00±0.101	5.65±0.030	100.05±0.092	99.30±0.003
F7	63.60±0.110	5.68±0.020	103.11±0.063	103.7±0.020
F8	65.00±0.106	5.65±0.036	100.14±0.072	102.26±0.025
F9	68.42±0.085	5.61±0.025	100.20±0.057	104.7±0.03

Taste analysis:

Taste analysis is done by constituting one five members panel. Tastes of various formulations reported in the following table as per volunteer's opinion.

Sensory evaluation data of Paracetamol & N-Acetylcysteine Effervescent Tablets.

Formulatoins	Volunteer									Avg. Score
	I	II	III	IV	V	VI	VII	VIII	IX	
F1	4	3	3	4	3	5	3	3	4	3.55
F2	3	3	3	4	3	4	3	3	3	3.22
F3	2	3	3	3	2	3	4	3	3	2.28
F4	3	2	3	3	2	3	3	3	4	2.88
F5	3	2	2	2	3	2	2	2	1	2.11
F6	2	3	2	2	2	1	2	1	2	1.88
F7	1	1	2	0	1	2	1	0	1	1.00
F8	1	2	1	0	1	1	1	2	1	1.11
F9	2	1	1	0	1	1	2	1	1	1.11

All values are expressed as mean ± SD (n=3)

Stability data of formulation (F7) on 1st month.

Parameters	25^{0}C/60% RH	30^{0}C/65% RH	40^{0}C/75%RH
Descriptions	White or off white, flat round shped beveled effervescent tablets	White or off white, flat round shped beveled effervescent tablets	White or off white, flat round shped beveled effervescent tablets
Texture	Smooth	Smooth	Smooth
Average Weight	4.015	4.051	4.022
Average Thickness	5.80 mm	5.78 mm	5.81 mm
Average Diameter	25.25 mm	25.25 mm	25.25 mm
Disintegration time	64 sec	67 sec	62 sec
Hardness	6.7 kg/cm2	6.5 kg/cm2	6.3 kg/cm2
pH of 1 tablet solution	5.66	5.64	5.66
Assay			
a) Paracetamol	100.59%	100.11%	100.22%
b) NAC	100.48%	100.32%	100.31%

CONCLUSION

In the present study of Paracetamol with N-Acetylcysteine effervescent tablets were prepared by using Citric acid and sodium bicarbonate as an effervescent composition, PVP K30 was used as binder. Sucralose as sweetening agent, Sucrose as a filler and sweetening agent and orange, polomint & aniseed as flavor in different ratios and they were characterized for different physical parameters, taste evaluation and drug content studies to find the optimized formulation that shows fast disintegration to form a clear solution. Paracetamol is analgesic and used for For temporary relief of fever, minor aches, and pains. N-Acetylcysteine a precursor of the antioxidant enzyme glutathione. Acetylcysteine regenerates liver stores of glutathione.NAC is mucolytic and also used as Paracetamol poisoning antidote. From the flowability studies the results revealed that, the Angle of repose (2530^0), Carr's index (≤10%) and Hausner's ratio (1.00-1.11) indicates good-excellent flow properties of the powder mixture. DSC study revealed that there is no interaction between the drug and excipients. The DSC curve of the optimized formulation did not show any significant shift in the endothermic peak, indicating that there was no physical change in drug in the effervescent compacts. The formulations were studied for their physical properties like weight variation, hardness, solution time, friability, pH of solution, percent water content, and drug content uniformity they were complied with Pharmacopoeial limits. The average percentage deviation of all tablet formulations was found to be within the above mentioned limit and hence all formulations passed the uniformity of weight as per official requirements. The formulations were uniform in hardness, solution time, friability, pH of solution, percent water content, and drug content uniformity. From the hardness, solution time, pH of solution, sensory evaluation study and percent drug content studies, F7 was selected as optimized formulation due to its all over best properties as compared to other formulations.

The Effervescent tablet of Paracetamol and N-Acetylcysteine is a new pharmaceutical formulation to be taken orally and offering a considerable advantage: avoidance of gastro-intestinal disorders, to the limits of the possible. Another aspect of this invention is that the absorption of the active ingredient is faster when compared to the tablet form; consequently an enhanced bioavailability of the active ingredient is probable. As compared to the pure drug and marketed tablet, effervescent tablet of Paracetamol and N-Acetylcysteine displayed significantly effective, palatable with improved patient compliance. In conclusion, development of the effervescent compacts can be a promising alternative technique to other dosage forms. Effervescent tablets are an effective means of supplying medications specially in case of elderly and pediatric population. This type of formulation provides the patients with an easy-to-swallow product that is aesthetically pleasing (i.e. forms clear solution which have better taste and excellent palatability).

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