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DEVELOPMENT OF NON SODIUM EFFERVESCENT TABLET OF PARACETAMOL USING ARGININE CARBONATE

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ABSTRACT: Effervescent tablets or granules are uncoated and generally contain acidic substances and carbonate or bicarbonate which reacts rapidly to release carbon dioxide when dissolved in water. There are various advantages of effervescent formulations such as fast onset of action, good stomach tolerance, improves palatability, enhanced permeability, but a major problem which is associated with these formulations is their sodium content which is present in the form of sodium bicarbonate. According to various guidelines the per day sodium intake is advised to be limited by 2400 mg. This excess sodium would produce health complications particularly to cardiac and renal patients. The main objective of present work was to use a non-alkali carbonate to avoid the problems which may occur due to presence of alkali carbonates in effervescent preparations. Arginine carbonate was found to be a suitable carbonate source as it has an additional advantage of being an amino acid source. Arginine carbonate was produced in the laboratory by saturating the solution of arginine in DM water with carbon dioxide and then dried on Rotavapor (Buchi) at 40°C and used as carbonate source. The effervescent tablets of paracetamol were developed for quick onset of action using arginine carbonate as alkali and citric acid as acid source respectively. The product was evaluated employing parameters like micromeritic properties, dispersion time, and carbon dioxide evolved and other relevant parameters. The developed product exhibited dispersion time of about 1.6 min. The optimized formulation passed the short term stability study.

INTRODUCTION: Effervescent systems are fast disintegrating systems and possess various advantages over conventional tablet dosage forms [5]. They have a major disadvantage that every effervescent formulation available in the market contains sodium bicarbonate as carbon dioxide source.

According to various guidelines the per day sodium intake is advised to be limited by 2400 mg [2a].

The main objective of the present work was to replace the sodium bicarbonate with some non-alkali carbonate and to develop non sodium effervescent formulation which will offer all the benefits of effervescent formulation without any risk to the health and be especially suited for cardiac and renal patients.

Objective: Most of the effervescent preparation available in the market contains sodium bicarbonate as a source of carbon dioxide. According to various

guidelines the per day sodium intake is advised to be limited by 2400 mg. Excess amount of sodium than this limit is likely to produce health complications particularly cardiac and renal related problems. The sodium content of available effervescent preparation is estimated to about 150 - 800 mg per unit. The advantages of effervescent formulation are well established. However, sodium based effervescent formulation will pose a serious health threat due to excessive sodium load to the body.

The main objective of the present work was to replace the sodium bicarbonate with some non-alkali carbonate and to develop non sodium effervescent formulation which will offer all the benefits of effervescent formulation without any risk to the health and be especially suited for cardiac and renal patients.

It was thought worthwhile to develop non sodium effervescent tablet formulation of paracetamol which will produce quick onset of action yet will not excessively load sodium to the body system.

MATERIALS AND METHODS: Following materials were used as received from commercial suppliers: citric acid (Loba Chemie, Mumbai), Pearlitol® (Signet, Mumbai), l-leucine (National Chemicals, Vadodara), Paracetamol (Elder pharmaceutical, Mumbai), PVP K 30 (Buronyl chemicals, Mumbai).

Preparation of Arginine Carbonate:- For preparation of Arginine carbonate, arginine was dissolved in DM water and purged with carbon dioxide and it was purged until the solution become saturated with carbon di oxide, the saturation point was tested by constantly observing the change in pH, when the pH become constant, the addition of carbon dioxide was stopped; after saturation the solution was dried at 40°C using Rotavapour (Buchi). Arginine carbonate obtained from above procedure was used for further formulation development purpose as a source of carbonate [3].

Preparation of Non-Sodium Effervescent Tablet: - When arginine carbonate and citric acid were mixed at 70-90%RH, a premature reaction occurred between the acid and base with the release of water and carbon dioxide. To avoid this problem of premature reaction between acid and base the whole formulation development process was carried in a controlled humidity at 35% ± 5% RH using DEHUMIDIFIER (Harrison's dehumidifier, HDV-1500 S. No. 235[H]). At this humidity no premature reaction occurred and both acid and base components could be properly mixed without any problem.

All the excipients used in the preparation were water soluble in nature, so that they will not delay the acid base reaction and a clear solution will be obtained when the tablet is dipped in water before administration. Required quantities of Paracetamol, arginine carbonate (carbonate source), citric acid (acid source), pearlitol (diluent), PVP K30 (binder) and l-leucine (lubricant) were taken for selecting the method of preparation.

Direct compression, wet granulation and dry granulation methods were studied for formulating the tablets, and the dry granulation method was found to be most suitable method for preparation of the effervescent tablets.

Optimization of Excipients Concentration: - Different combinations of excipients were used in order to achieve a dispersion time of less than 2 min. The 5% concentration of binder was initially found suitable for the formulation. It was found that nearly 30% of pearlitol was required to keep the formulation submerged in water. The final formulation batch was selected on the basis of the lowest dispersion time. Results obtained were reported in **table 1**. The optimized formula obtained is given in **table 2**.

PREPARATION AND EVALUATION OF OPTIMIZED FORMULATION BATCHL The optimized formulation batch was prepared by dry granulation method and evaluated for various parameters like friability, weight variation, content uniformity, angle of repose, compressibility index, and properties related to effervescent tablets like total dispersion time, carbon dioxide evolution by gravimetric method, and change in pH of solution.

Friability of optimized batch: Ten tablets were taken and weighed accurately and were placed in Roche friabilator and it was rotated with a rate of 25 rpm for 4 min., after that the dust was removed from the tablets and the weight of all the tablet was taken and from that the percent friability was calculated.

TABLE 1: EFFECT OF INCREASING SERIALLY INCREASING CONCENTRATION OF ARGININE CARBONATE ON THE DISPERSION TIME OF TABLET (WITH SOME CHANGE IN CONCENTRATION OF SOME EXCIPIENTS ALSO)

S. No.	Ingredients	Batch No.									
		ARG 1	ARG 2	ARG 3	ARG 4	ARG 5	ARG 6	ARG 7	ARG 8	ARG 9	ARG 10
		QUANTITY									
1.	Arginine Carbonate	mg	700 mg	800 mg	900 mg	1000 mg	1100 mg	1100 mg	1200 mg	1300 mg	1300 mg
2.	Citric acid	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
3.	Pearlitol	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg
4.	Drug	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
5.	Binder	5%	5%	5%	5%	5%	5%	4%	5%	5%	3%
6.	Lubricant	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
REMARK		Dipped	Dipped	Dipped	Dipped	Dipped	Dipped	Dipped	Dipped	Dipped	Dipped
DISPERSION TIME		3min 45sec	3min 40sec	3min 34sec	3 min 25sec	2 min 10 sec	4 min 12 sec	2min 51sec	2 min 30 sec	2 min 42 sec	1 min 40 sec

TABLE 2: FORMULA OF FINAL BATCH

S. No.	Ingredient	Quantity
1.	Paracetamol	500 mg
2.	Arginine carbonate	1300 mg
3.	Citric acid	500 mg
4.	Pearlitol	900 mg
5.	PVP K30	105 mg
6.	L-leucine	175 mg

Flowability and compressibility of granules of optimized batch: Compressibility index and Hauser's ration were calculated by determining the bulk density and the tapped density.

Hausner's ratio = D_f / D_o,

Where, D_o = Bulk density, D_f = Tapped density

Compressibility Index = $\{(V_o - V_f)/V_o\} \times 100$,

Where, V_o = Initial volume of untapped granules, V_f = Tapped volume

Angle of repose was also determined in order to determine the flow property of the granules.

Weight variation, content uniformity of optimized batch: In order to analyze the uniform distribution of active ingredients in the final formulation parameters like weight variation, content uniformity were studied. For weight variation test, twenty tablets were taken and weighed individually. Their average weight was and the percent deviation from average was calculated. Not more than 2 tablets should be out of range.

For uncoated tablets having average weight of more than 250 mg, deviation up to 5% weight from average weight is allowed [6].

For content uniformity test ten tablets from the batch were taken at random and were crushed individually and from each, powder equivalent to 50 mg of drug was taken and dissolved in water. The resulting solution was suitably diluted and analyzed spectrophotometrically for drug content at 244nm.

Carbon di oxide loss by gravimetric method: The tablet was accurately weighed and added to weighed quantity of approx. 200 g of water. The CO_2 gas evolved which led to the reduction in weight of total quantity. The final weight was noted and reduction in weight was calculated.

Determination of change in pH: The pH of demineralized water was noted initially, then the developed tablet was added to it and after completion of evolution of carbon dioxide, the pH of the fluid was again noted.

Stability Studies: Studies were conducted to test the physical and chemical stability of the developed products employing the parameters like change in colour; change in weight due to any premature reaction; the pH when formulation is added in water; the dispersion time; and drug chemical stability.

As the formulations are very much sensitive to moisture for the stability studies they were kept in an air tight container and then they were kept at different temperature for stability studies.

RESULT AND DISCUSSION: Effervescent formulations are rapidly disintegrating oral dosage forms containing mixture of alkali carbonate/bicarbonate and organic acid. When water is added to these formulations, a suspension or solution is formed with CO_2 evolution. The resulting suspension or solution develops a pleasant taste and ease in swallowing. They were used from many years because of their fast onset of action and increased patient compliance.

Previously these formulations were formulated using water soluble drugs but later on water insoluble drugs were also incorporated. These formulations have a major disadvantage that they contain large amount of sodium in the form of sodium bicarbonate, whose excess can cause cardiac complexities in sensitive patients. This drawback of effervescent formulation limits its use in these patients. So, the objective of present work was focused to replace the alkali carbonate/bicarbonate with non-alkali carbonate/ bicarbonate focused for developing effervescent formulation.

To rule out the physical incompatibility between the drug and the excipient, blends of the drug and excipients were kept under varied temperature conditions. Paracetamol was found to be compatible with the excipient selected in the present work.

Water soluble excipients were used for development of effervescent formulation of paracetamol to produce a clear transparent solution upon disintegration and carbon dioxide evolution from adding the formulation to water. Water soluble binder i.e. Polyvinyl pyrrolidine K30 was used and water soluble lubricant i.e. l-leucine selected for formulation development. Water soluble diluent i.e. spray dried mannitol (Pearlitol) was selected from the various water soluble diluents. Citric acid, commonly used acid in effervescent formulation was selected for the development of present formulation.

Effervescent formulations comprising various ratios of these excipients were prepared and evaluated for their water dispersion time. The formulation having dispersion time less than 2 min. was used for further development.

Evaluation of Granules of Optimized batch: The granules of optimized batch prepared by dry granulation method were evaluated for their various micromeritic properties like angle of repose, bulk density, tapped density, hausner ratio, and % compressibility. The results obtained were reported in **table 3**.

TABLE 3: MICROMERITIC PROPERTIES OF SLUG GRANULES.

S. No.	Bulk density	Tapped density	Hauser ratio	Compressibility index	Angle of repose
1.	0.562 g/ml	0.649 g/ml	1.154	13.483	31.18

Evaluation of Compressed tablets of Optimized batch: The compressed tablets of optimized batch were tested for various tablet evaluation parameters like friability, content uniformity and weight variation, in this batch the friability was 0.933% and thus the batch passed the friability test [6]. The drug content of the tablets was found to be in the range of 95.5% to 103.8 % which was within the acceptable limit [6]. The batch thus passed the content uniformity test.

The results of weight variation test were reported in **table 4** and the result shows that the batch passed the weight variation test.

TABLE 4: WEIGHT VARIATION TEST FOR THE OPTIMIZED BATCH OF EFFERVESCENT TABLET FORMULATION OF PARACETAMOL

S. No	No. of tablets	Average weight	Weight of Individual Tablet		Remark
			Lowest	Highest	
1.	20	3.45g	3.30	3.61	Test pass

The tablets were then evaluated for various parameters which are used for the evaluation of effervescent tablet like balance test method, dispersion time and change in pH. Results of these tests are shown in **table 5**.

Thermal stability testing of Optimized batch: As effervescent formulation are very much sensitive towards moisture and they may undergo effervescence even in presence of little moisture, thus the stability studies of the optimized batch was

performed in a moisture impermeable packaging system at different temperatures viz. room temperature and at 40˚C. The results of stability studies were shown in **table 6** and these result shows that these preparations were stable in terms of drug content, dispersion time, change in pH and loss in weight at room temperature for one month period when packaged in a moisture impermeable system.

TABLE 5: EVALUATION OF DEVELOPED EFFERVESCENT FORMULATION OF PARACETAMOL TABLET

S. No.	Weight of tablet	Dispersion time	Carbon dioxide evolved	Change in pH		
				Initial pH	Final pH	Change in pH
1.	3.32 g	1.55 min.	0.59 g	6.55	6.56	0.01
2.	3.39 g	1.62 min.	0.56 g	6.55	6.57	0.02
3.	3.35 g	1.60 min.	0.57 g	6.55	6.57	0.02
4.	3.43 g	1.63 min.	0.56 g	6.55	6.58	0.03
5.	3.50 g	1.73 min.	0.56 g	6.55	6.60	0.05
6.	3.45 g	1.65 min.	0.56 g	6.55	6.59	0.04
7.	3.53 g	1.76 min.	0.54 g	6.55	6.60	0.05
8.	3.36 g	1.58 min.	0.58 g	6.55	6.56	0.01
9.	3.46 g	1.60 min.	0.57 g	6.55	6.58	0.03
10.	3.46 g	1.66 min.	0.56 g	6.55	6.59	0.04
Average		1.63 min.	0.565 g	6.55	6.58	0.03

TABLE 6: STABILITY DATA OF DEVELOPED OPTIMIZED FORMULATION OF EFFERVESCENT TABLET OF PARACETAMOL USING ARGININE CARBONATE

Formulation Batch no.: OF-ARG

Pack : Tablets were wrapped in aluminium foil completely and kept in an air tight container

Test parameters	Stability conditions				
	In house limits	Room temperature		40˚C	
		2 weeks	1 month	2 weeks	1 month
Description	White color tablet	White color tablet	White color tablet	White color tablet	White color tablet
Weight	3.45 g	3.46 g	3.46 g	3.45 g	3.45 g
Dispersion time	1.63 min.	1.61 min.	1.66 min.	1.66 min.	1.7 min.
Change in pH of solution	0.03	0.03	0.04	0.04	0.04
Carbon dioxide release	0.565 g	0.56 g	0.55 g	0.56 g	0.55 g
Drug content	99.65%	99.46%	98.32%	97.68%	97.16%

CONCLUSION: Based on the above findings it can be concluded that arginine carbonate is a better alternative of sodium bicarbonate for the preparation of non-sodium effervescent formulations as it does not load any excess sodium to the body. It can also be concluded that l-leucine and PVP K30 can be used as lubricant and binder respectively in these types of formulations.

The developed formulations will have acceptability in all segment of population including cardiac and renal patients.

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Reviewer's recommendations:

1. **Abstract should not contain references.**
2. **References in main text should start with numeral 1.**
3. **In Table 1, ARG1 Column, no quantity value given.**
4. **Check for spelling, grammar and punctuation errors.**
5. **Check for references.**