Preparation of Effervescent Granules from an Antidiarrhoeal Unani Powder and Defining its Physicochemical Characters

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Abstract

Diarrhoea is worldwide health problem for which a number of drugs are available in Unani and other traditional systems of medicine. However the low patient compliance is a major problem with traditional drugs requiring the optimization of various dosage forms. In the present study an age-old Unani compound powder was converted into effervescent granules to improve its palatability and the kinetics. Further, in order to determine the quality standards of the new dosage form the physicochemical studies were also carried out. The data generated in respect of its physicochemical attributes may be used for future reference.

Keywords: Anti-diarrhoeal effervescent granules (ADEG), Standardization, Diarrhoea.

Introduction

Effervescent granules usually consist of acid substances and carbonates or hydrogen carbonates which react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration (Anonymous, 2007; 2009). According to the European Pharmacopoeia, the effervescent forms are defined as those granules or tablets that are to be dissolved in water before administration. 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. Disintegration of the tablets or granules usually occurs within three minutes or even less, due to the evolution of carbon dioxide (Parikh, 2005).

The first effervescent preparation was invented over two centuries ago in the official compendia. Effervescent granules and tablets have become popular as the dosage forms due to their rapid solubility and consumption just by drinking the glass of water in which they have been dissolved. Effervescent forms have many benefits over conventional pharmaceutical forms. They bear a pleasant taste and mask the bad taste of certain drugs. This could help to avoid the gastric side effect of certain drugs. Effervescent dosage form is more consumers compliant because of its easy usage and attractive form (Parikh, 2005).

A number of Unani drugs are used to manage acute and chronic diseases but in many cases patients compliance remains a problem because of the conventional dosage forms which may not be convenient to use for every patient. An important antidiarrhoeal Safoof (ADS) mentioned in Akseere Azam (Khan,

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2011) is commonly prescribed by the physicians of Unani medicine. Although physicians find it very effective in the management of diarrhoea and dysentery but they are bound to opt for other options of even low potency in case of the children, aged people and many other patients who find it difficult to swallow the powder. The present study was therefore designed to convert ADS into Anti Diarrhoeal Effervescent Granules (ADEG) with an aim to make it more palatable. This will also make the therapeutic application of the drug wider.

Materials and Methods

Procurement of raw drugs

All the raw drugs (*Aegle marmelos, Coriandrum sativum, Cuminum cyminum, Foeniculum vulgare, Vateria indica and Zingiber officinale*) were procured from the approved raw drugs dealer of Bengaluru. Identification and authentication was conducted by botanist, Prof. K. Ravikumar, Centre for Repository of Medicinal Resources (C-RMR), Trans-Disciplinary University (TDU), Attur, Bengaluru. The voucher specimens of the samples have been deposited in the museum of Institute of Trans-Disciplinary Health Sciences and Technology, Bengaluru.

Procurement of chemicals

All the excipients used in effervescent granules were procured from Bengaluru.

Preparation of ADEG

All the crude drugs/ingredients of ADEG were cleaned and allowed to dry in shade. Thereafter all the ingredients were separately put in electrical grinder to make coarse powder. The powder of all the ingredients wee then mixed together in equal proportions. After that, extract of above compound powder was prepared in distilled water by using Soxhlet apparatus at 80°C. Extracted material was filtered and then dried on water bath. After drying, percentage of extractive value was calculated. This extract was ground in pestle and mortar and stored in an air tight glass container at room temperature for further use. Sodium bicarbonate, citric acid, tartaric acid, refined sugar and flavour (Table 1) were used as excipients. Thereafter ADEG was prepared by hot melt granulation method as described in pharmacopoeias and stored in air tight glass container.

Physico-chemical Evaluation of Anti-Diarrhoeal Effervescent Granules

The physico-chemical studies of ADEG were carried out in the laboratory of Dept. of Ilmul Saidla, NIUM, Bengaluru, which included (a) Organoleptic properties like

appearance, colour, smell and taste (b) Extractive values (c) Ash values (d) Moisture contents (e) Loss of weight on drying (f) Angle of repose (g) Bulk density (h) Tapped density (i) Carr's index (j) Hausner's ratio (k) pH value (l) Effervescent cessation time (m) CO_2 gas content (n) Qualitative estimation (o) Quantitative estimation (p) Dissolution time and (q) TLC finger printing.

Determination of Organoleptic Properties

Organoleptic properties of ADEG such as appearance, colour, odour and taste were noted.

- Appearance: Small quantity of ADEG was taken and uniformity of granular size and amorphous or crystalline nature was observed.
- Colour: Five gram of ADEG was taken into watch glass and placed against white background in white tube light. The colour of effervescent granules was noted by using Pantone colour chart.
- Odour: A small quantity of the ADEG was rubbed between the thumb and index ûnger and inhaled. First, the strength of the odour like none, weak, distinct, strong etc was determined and then the odour sensation like aromatic, fruity, musty, mouldy, rancid, etc was evaluated.
- Taste: A pinch of ADEG was examined for the taste on the upper surface of the tongue and one minute time was given to decide the taste.

Determination of alcohol-soluble matter

Five gm of ADEG was placed in a glass-stopper conical flask. Macerated with 100 ml of Ethyl alcohol for six hours shaking and then allow standing for 18 hours. Shake well and filtered rapidly through a dry filter paper. 25 ml of the filtrate was transferred to a previously weighed and tarred flat-bottom petridish and evaporate to dryness on a water bath. This filtrate was dried at 105°C for six hours, cooled in a desiccator for 30 minutes and weighed without delay. The percentage of alcohol soluble matter was calculated with reference to the amount of drug taken (Anonymous, 1998; 2009).

Determination of water-soluble matter

The percentage of water soluble matter was determined as above by using chloroform water instead of ethanol (Anonymous, 1998; 2009).

Determination of successive extractive values

The extractive values of ADEG in different solvent viz. petroleum ether, chloroform and ethanol were carried out in soxhlet extractor. Five gm of Anti-diarrhoeal

Effervescent granules was successively extracted with 150 ml of each solvent for six hours. The extracts were filtered with filter paper and transferred to a previously weighed and tarred flat-bottom petridish and evaporated for complete drying on a water bath. The successive extractive values were determined with reference to the weight of ADEG (% w/w) (Anonymous, 2009).

Determination of total ash

Three samples of two gm ADEG were incinerated in tarred silica dishes at a temperature not exceeding 450°C until free from carbon, cooled and weighed. The percentage of total ash was calculated with reference to the ADEG (Anonymous, 1998; 2006).

Determination of acid insoluble ash

The total ash of ADEG was boiled with 25 ml of diluted hydrochloric acid for five minutes and filtered. The insoluble matter was collected on an ash less filter paper, washed with hot water and ignited at a temperature not exceeding 450°C for one hour and weighed after cooling. The percentage of acid-insoluble ash was calculated (Anonymous, 1998; 2006).

Determination of water soluble ash

The total ash was boiled with 25 ml of distilled water for five minutes and filtered. The insoluble matter was collected on an ash less filter paper (Whatman), washed with hot water and ignited at a temperature not exceeding 450°C for one hour. The weight of insoluble ash was subtracted from the weight of total ash, giving the weight of the water soluble ash (Anonymous, 1998; 2006).

Moisture content

The moisture content was determined by Toluene Distillation method. 10 gm of ADEG was taken in a flask and 75 ml of Toluene was added to it. Distillation was carried out for five hours. The volume of water collected in the receiver tube was noted and the percentage of moisture was calculated (Afaq *et al*., 1994).

Determination of loss of weight on drying

Four gm of ADEG was taken, spread uniformly and thinly in a shallow petridish. It was heated at a regulated temperature of 105°C for five hours, cooled in desiccator and weighed. The process was repeated many times till two consecutive weights were found constant. The percent loss in weight was calculated with reference to initials weight of ADEG (Anonymous, 1998; Afaq *et al*., 1994).

Determination of angle of repose

The angle of repose was determined by using fixed funnel method. The height of the tip of funnel was fixed two cm above the horizontal surface. A graph paper was placed below the funnel on the table. The ADEG was allowed to flow through the funnel freely on to the surface until the apex of the conical pile just touches the tip of the funnel. The diameter of the powder cone base was measured and the angle of repose was calculated by using the following formula (Anonymous, 2007).

$$\tan \theta = \frac{\text{height of funnel}}{0.5 \text{ base}}$$

Determination of bulk density

An accurately weigh ADEG was introduced into a dry 100 ml graduated glass cylinder. The test sample was carefully levelled without compacting and the unsettled apparent-volume (Vo), was observed. The bulk density was calculated by using the following formula:

$$\rho b = \frac{M}{V_0} \text{ gm/ml}$$

Where; ρb = Apparent bulk density,

M = Weight of sample,

Vo = Apparent (untapped) volume of sample (Anonymous, 2006; Gupta, 2013).

Determination of tapped density

After observing the bulk density by the above method, sample containing graduated cylinder was tapped firstly for 500 times, followed by an additional taps of 750 and 1250 times in Tapped Density Apparatus (TD 1025) Lab India, until the difference between the two succeeding measurement is less than 2% and then tapped volume (Vf), was measured to the nearest graduated unit. The tapped density was calculated in gm/ml, using the following formula:

$$\rho tap = \frac{M}{Vf} \text{ gm/ml}$$

Where: ρtap = Tapped density,

M = Weight of sample,

Vf = Tapped volume of sample (Anonymous, 2006; Gupta, 2013).

Determination of Carr's index

Carr's index was calculated by using the following formula:

$$\text{Compressibility index} = \left[\frac{\text{Tapped Densit } (\rho tap) - \text{Bulk Density } (\rho b)}{\text{Tapped Density } (\rho tap)} \right] \times 100$$

Where; ρb = Bulk Density,

ρtap = Tapped Density (Anonymous, 2006; Gupta, 2013).

Determination of Hausner's ratio (Anonymous, 2006; Gupta, 2013)

It was calculated by the following formula:

$$\text{Hausner's Ratio} = \frac{\text{Tapped Densit } (\rho tap)}{\text{Bulk Density } (\rho b)}$$

Determination of pH

Five gm of ADEG was dissolved in 200 ml purified water in a beaker. After completing the effervescence, pH was measured at 25°C ± 1°C by using pH meter).

Determination of effervescent cessation time

Five gm of ADEG was placed in 200 ml purified water containing beaker at 25°C. When a clear solution was obtained indicating that effervescence has been finished, this time was noted (Aslani, 2013).

Determination of CO_2 gas content

100 ml of 1N sulphuric acid was taken in a beaker and weighed. Five gm of ADEG was dissolved in it. After full dissolution, this solution was re-weighed and change in weight was observed. Decrease in weight, indicates the CO_2 value in a dose (Aslani 2013_a).

Qualitative Estimation

Qualitative estimation of alkaloids, tannins, flavonoids, glycosides, phenols and terpenoids was done by the methods described in Physicochemical Standards of Unani Formulations, Part IV (Anonymous, 2006).

Quantitative Estimation

Tannin Assay

Preparation of drug infusion: Three gm of ADEG was dissolved in 250 ml distilled water at room temperature and then filtered.

Quantitative estimation of Tannin

For the analysis of tannin content in ADEG, 25 ml of ADEG infusion, prepared by the method given above, was taken into one litre conical flask, then 25 ml of indigo solution and 750 ml distilled deionised water were added. 0.1 N aqueous solution of $KMnO_4$ was used for titration until the blue coloured solution changed to green. Then few drops were added until solution turned into golden yellow colour. The volume of 0.1 N $KMnO_4$ solution required for titration was recorded. For blank test the mixture of 25 ml Indigo carmine solution and 750 ml distilled water was titrated with 0.1 N $KMnO_4$ solution and the volume required for titration until solution turned into golden yellow colour was recorded.

Calculation

The tannin content (T %) in the sample was calculated as follows:

$$T(\%) \quad \frac{(V-V_0) \times 0.004157 \times 250 \times 100}{g \times 25}$$

Where:

T (%) = Tannin quantity in percentage

V = Volume of 0.1 N aq. solution of $KMnO_4$ for the titration of the test sample in ml.

V_o = Volume of 0.1 N aq. solution of $KMnO_4$ for the titration of the blank sample in ml.

0.004157 = Tannin equivalent in 1 ml of 0.1 N aqueous solution of $KMnO_4$

g = Mass of the sample taken for the analysis in gm

250 = Volume of the volumetric flask in ml (Atanassova, 2009)

TLC finger printing

For the separation of different phytochemical constituents in ADEG, the chloroform extract was spotted manually using a capillary tube on pre-coated silicagel TLC plates 60 F 254 (layer thickness 0.25). The spotted plates were put into a solvent system of toluene: Ethyl acetate (8:2). After the separation of constituents, the plate was dried at 110°C. After drying, spray of vanillin sulphuric acid reagent was used to visualize the spots. The colour of the spots was noted and R_f value was calculated.

Determination of Dissolution time

Medium: 0.1N Hydrochloric acid buffer pH 1.2 solution was prepared (8.5 ml HCl diluted in 1000 ml of distilled water) as a dissolution medium.

Preparation of standard stock solution: One gm of accurately weighed ADEG was dissolved in 100 ml of buffer medium in 250 ml beaker and filtered to make 10 mg/ ml.

Preparation of standard curve: From the above standard stock solution aliquots of 0.05, 0.1, 0.2, 0.4, 0.6, 0.8 and 1 ml was taken into different 10ml volumetric flask and diluted in buffer to get concentration from 12µg/ml- 1mg/ml.

Firstly, blank buffer solution was scanned in UV visible Spectrophotometer (LAB India) between 190nm to 900nm wavelength to get base line. Then, above prepared solutions was scanned to get ë -max.

In-vitro release study was carried out using 900 ml 0.1N Hydrochloric acid buffer pH 1.2 solution. The Basket was rotated at 100 rpm. The medium was set at 37 ± 0.50°C. At 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 minutes, 10 ml aliquot of the solution was collected from zone midway between the surface of dissolution medium and the top of rotating basket not less than one cm apart from the vessel wall of the dissolution apparatus and was replaced with fresh dissolution medium. The withdrawn samples were filtered through Whatman filter paper and analyzed by an UV spectrophotometer (Lab India) at 370 nm using hydrochloric acid buffer pH 1.2 as a blank (Basak, 2006; Tekade, 2014).

Results and Discussion

The organoleptic properties of ADEG were found to be light brown in colour, amorphous granules with acidic lemon taste (Table 2, Fig 1). These are very important for drug identification and quality assurance and also necessary for patient compliance; the acceptance among the consumers automatically gets increased if these properties are good. The alcohol and water soluble matter of ADEG were found to be 24.814 ± 0.10% and 71.574 ± 0.19%, respectively (Table 3). This shows that the constituents of the drug are more soluble in alcohol than water. The mean percentage of successive extraction values was found to be

Table 1: Composition of Anti-diarrhoeal Effervescent Granules

S.No.	Ingredients	Property	Quantity (%)
1.	Extract	Active ingredient	27.1
2.	Sodium bicarbonate	Alkalizing agent	31
3.	Citric acid	Acidifying agent	14
4.	Tartaric acid	Acidifying agent	16
5.	Refined sugar	Sweetener	11
6.	Flavour (lemon)	Flavouring agent	0.9

Table 2: Organoleptic Properties of ADEG

Appearance	Amorphous granules
Colour	Light brown (1365 on panton colour chart)
Odour	Mild pungent lemon
Taste	Acidic

Table 3: Physicochemical Parameters of ADEG

Parameters	Samples			Mean ± SEM
	1	2	3	
Alcohol soluble matter (%)	24.680	24.735	25.029	24.814 ± 0.10
Water soluble matter (%)	71.522	71.927	71.274	71.574 ± 0.19
Successive Extractive Values:				
Petroleum ether (%)	0.06	0.08	0.06	0.06 ± 0.00
Chloroform (%)	0.16	0.18	0.14	0.16 ± 0.01
Ethyl alcohol (%)	5.52	5.74	5.85	5.70 ± 0.09
Ash Values:				
Total ash (%)	25.35	25.62	27.19	26.05 ± 0.57
Acid insoluble ash (%)	3.35	2.62	3.09	3.02 ± 0.21
Water soluble ash (%)	22.30	21.37	20.95	21.54 ± 0.39
Moisture content (%)	2.50	2.99	2.49	2.66 ± 0.16
Loss of weight on drying (%)	2.769	2.950	2.850	2.856 ± 0.05
pH Value:	5.85	5.87	5.84	5.85 ± 0.00
Effervescent cessation time (sec)	135	135	140	136.66 ± 1.66
CO_2 gas content (%)	22.32	22.14	22.04	22.166 ± 0.08
Angle of repose	34.5901	34.3063	33.8692	34.2552 ± 0.20
Bulk density (gm/ml)	0.5000	0.5000	0.5000	0.5000 ± 0.00
Tapped density (gm/ml)	0.5714	0.5714	0.5687	0.5705 ± 0.00
Carr's index	12.5000	12.5000	12.0800	12.36 ± 0.14
Hausner's ratio	1.1428	1.1428	1.1374	1.141 ± 0.00
Tannins (%)	3.60	3.74	3.74	3.69 ± 0.04

Figure 1: Laboratory Sample of Antidiarrhoeal Unani Effervescent Granules (ADEG)

0.06 ± 0.00, 0.16 ± 0.01, 5.70 ± 0.09 in petroleum ether, chloroform and ethanol, respectively (Table 3). This is an important parameter to evaluate the quality and purity of the drugs. The chemical constituents of the drugs are extractable in different solvent systems. These values are high in particular solvent in which the drug constituents are maximally soluble.

The mean percentage of total ash, acid insoluble ash and water soluble ash were found to be 26.05 ± 0.57, 3.02 ± 0.21 and 21.54 ± 0.39, respectively (Table 3). Total ash includes both "physiological ash", which is derived from the plant tissue itself and "non-physiological ash" which is residue of the extraneous matter adhering to the plant surface. Acid insoluble ash includes the amount of silica present, especially as sand and siliceous earth (Bele *et al.*, 2011). The mean percentage of moisture content was found to be 2.66 ± 0.16 (Table 3). An excess of water in medicinal plant materials provides good media for microbial growth, and deterioration following hydrolysis (Bele *et al.*, 2011). The mean percentage of loss of weight on drying was found to be 2.856 ± 0.05 (Table 3).

pH value of ADEG was found to be 5.85 ± 0.00 (Table 3). The finding will help in deciding the kinetics of the drug. The effervescence time is the time that the solution becomes free of particles; the acceptable range of this time is under three minutes (Aslani, 2013). The mean value of effervescent cessation time of ADEG was found to be 136.66 ± 1.66 sec., which is in the prescribed range (Table 3). The CO_2 content changes the taste and effervescence time (Aslani, 2013). The mean percentage of CO_2 gas content was found to be 22.166 ± 0.08 (Table 3, Fig. 8). Angle of repose was found to be 34.2552 ± 0.20 (Table 3). The result shows that inter-particular friction of particles of ADEG is low which shows its good flow ability.

The mean values of bulk density and tapped density were found to be 0.5000 ± 0.00 and 0.5705 ± 0.00, respectively (Table 3). Bulk and tapped density are very important in deciding the size of containers needed for handling, shipping, and storage of raw material and blend (Sandhya *et al*, 2012). The mean values of carr's index and hausner's ratio were found to be 12.36 ± 0.14 and 1.141 ± 0.00, respectively (Table 3) which is graded as passable flow ability. In theory, the less compressible a material the more flow-able it is (Anonymous, 2006). In qualitative estimation of ADEG; alkaloids, trannins, flavonoids, glycosides, phenols and terpenoids were found to be present (Table 4).

Tannins are astringent, bitter plant polyphenols that either bind and precipitate or shrink proteins. The astringency from the tannins is that which causes the dry and puckery feeling in the mouth on consumption. Tannins may be employed medicinally in anti-diarrheal, haemostatic, and anti-haemorrhoidal compounds. Tannins have been used for immediate relief of sore throats, diarrhoea, dysentery, haemorrhage, and skin ulcers (Ashok, 2012). The mean percentage of tannin was found to be 3.69 ± 0.04 (Table 3).

TLC and the Rf value calculated on the basis of spots detected is one of the important parameters used for detecting the adulteration and deciding the quality of drugs, as there will be variation in number of spots and Rf values in case of adulteration or poor quality of the drug. Five spots were found in chloroform extract of ADEG. The R_f values of five spots were found to be 0.12, 0.25, 0.43, 0.58 and 0.65 and the colour of spots were light blue, purple, blue, sky blue and dark purple respectively (Table 5, Fig 2).

Dissolution test is required to study the drug release from the dosage form and its *in vivo* performance. Dissolution test is used to assess the batch to batch

Table 4: Qualitative Estimation of ADEG

S.No.	Medicinal constituents	Presence
1.	Alkaloids	+
2.	Flavonoids	+
3.	Glycosides	+
4.	Phenols	+
5.	Resin	_
6.	Steroids	_
7.	Tannins	+
8.	Terpenoids	+

Table 5: TLC of ADEG

Extract	Solvent	No. of spots	R_f Value	Colour
Chloroform	Toluene: Ethyl acetate (8:2)	five	0.12, 0.25, 0.43, 0.58 and 0.65	Light blue, Purple, Blue, Sky blue and Dark purple

Table 6: Dissolution Time of ADEG

S.No.	Time (min)	Absorbance at 370 nm
1.	1	0.720
2.	2	0.764
3.	3	0.910
4.	4	0.920
5.	5	0.920
6.	6	0.920

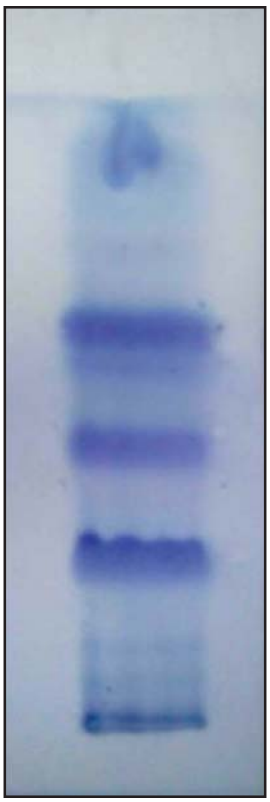

Figure 2: TLC of Antidiarrhoeal Unani Effervescent Granules (ADEG)

quality of drug product. The development and validation of dissolution procedures is of predominant importance in quality control. It is commonly used as a predictor of the *in vivo* performance of a drug product (Vaghela, 2011). The absorbance of ADEG was found maximum (0.920) at four minutes (Table 6).

Conclusion

Newly developed ADEG may be used in place of anti-diarrhoeal *Safoof,* for better patient compliance. The developed physicochemical standards of ADEG may be used for future reference.

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