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Formulation of solid dosage forms using natural ingredients and novel method development for estimation of drug content

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Abstract

The study is based upon the formulation of solid dosage forms, using natural ingredients and a novel method development for the estimation of individual ingredients in various combination units. Tablets of analgesic drug mafenemic acid in combination with dicyclomine, a smooth muscle relaxant was prepared. A hepatoprotective agent DL-methionine was also incorporated in the formulation. Enhancement of bioavailability of analgesic tablets by introducing the seeds of *Lallemantia royleana* Benth (commonly known as Balanga) was achieved, accompanied with the estimation of the amount of methionine, incorporated in the formulation. The mathematical tool of orthogonal polynomials was implemented for the above estimation of percentage purity of a particular ingredient in the above complex formulation.The novel formulation is evaluated in terms of its bioavailability by comparing the parameters like disintegration time and dissolution time, with that of the standard formulations. The above assessment was carried out to establish the role of the natural disintegrant used. There are many methods to enhance bioavailability; one of the methods is the reduction of disintegration time. Balanga seeds are used for the above purpose as the seeds are known to contain plenty of mucilage within its chemical constituents. The mucilage absorbs water by imbibition and helps in tablet disintegration.

Key words: Balanga seeds, Bioavailability, Disintegration time, Orthogonal polynomials, Hepatoprotective

Introduction

Disintegration: It can be defined as the process by which the tablet breaks down or loses cohesion. It is the time required for the tablet to break down into aggregates. Several mechanisms of tablet disintegration have been proposed. Eventhough these concepts are listed separately. Interrelationships probably occur in almost all tablet formulations (Anonymous, 2008).

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(i) Effect of water absorption

The water absorbed by the tablet initiate disintegration, but this depends on the solubility of the drug and other ingredients present.

(ii) Swelling

The grains of the disintegrant, particularly of starches, swell in the presence of water and exert pressure on the granules to force them apart. Shangraw *et al.* (1980) reported that tablets of water insoluble drugs disintegrated faster with starches than those of water soluble drugs due to the diminished water absorption capacity of the starches in the latter case.

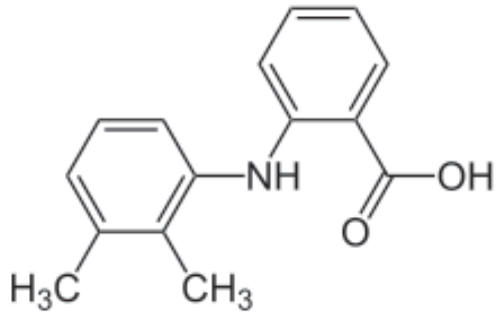
Imbibition is defined as the displacement of one fluid by another immiscible fluid. This process is controlled and affected by a variety of factors. The capillary number (Ca)

and the mobility ratio (M) have the greatest importance. It is also defined as the phenomenon by which the living or dead plant cells absorb water by surface attraction.

Porosity of tablets: It has been shown that penetration of water into a tablet is proportional to its mean pore diameter or porosity. The porosity and permeability of tablets decrease as the tabletting pressure is increased, and as the porosity decreases, the disintegration time increases. Though, no quantitative relationships have been reported between disintegration and penetration times, generally short disintegration times are associated with rapid fluid penetration and drug absorption. Thus, the above parameter is related directly to the absolute bioavailability of drugs **(**Shargel, 1999 and Graham Lappin, 2006).

***Lallemantia royleana* Benth (Commonly known as Balanga)**

Chemical constituents: 10.8% of fixed oil is present. Verbenone (16.4%) and trans-carveol (9.8%) were the major components of the oil (Braj Kishore Malavya and Shikibhushan Dutt.,1941). The exact chemical constituents responsible for the specific therapeutic activity are not known. When moistened with water, the seeds become voluminous and form translucent mucilage.



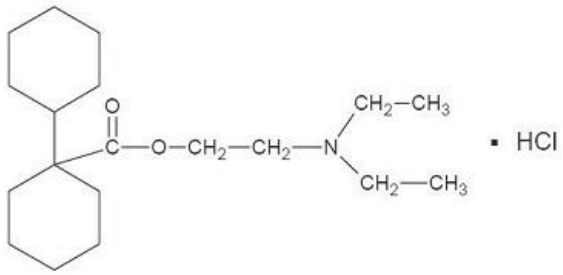
Mafenemic Acid

Systematic (IUPAC) name 2-(2,3-dimethylphenyl) amino benzoic acid

Mefenamic acid binds the prostaglandin synthetase receptors COX-1 and COX-2, inhibiting the action of prostaglandin synthetase. As these receptors have a role as a major mediator of inflammation and/or a role for prostanoid signalling in activity-dependent plasticity, the symptoms of pain are temporarily reduced (Cryer and Feldman,1998).

Dicyclomine hydrochloride is an antispasmodic and anticholinergic (antimuscarinic) agent available in various dosage forms.

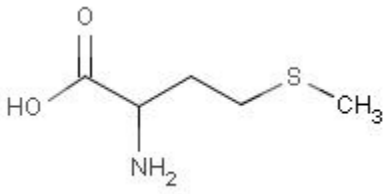
Chemically, BENTYL (dicyclomine hydrochloride) is [bicyclohexyl]-1-carboxylic acid, 2-(diethylamino) ethyl ester, hydrochloride with the following chemical structure:



Dicyclomine hydrochloride

Dicyclomine hydrochloride occurs as a fine, white, crystalline, practically odorless powder with a bitter taste. It is soluble in water, freely soluble in alcohol and chloroform, and very slightly soluble in ether (Chananont and Hamor,1981).

Methionine



Chemical structure for DL-METHIONINE

Methionine may be one of the earliest organic substances, formed in evolution. In man, it is essential as a donor of the critical methyl (CH_3) group (Banesh,1978) and as a sulphur donor. The CH_3 group comes from its activated form, SAM (S-adenosyl N-methionine), and goes into the formation of important compounds like choline (in bile acids, phospholipids), creatine (in muscles), epinephrine (a neuro-transmitter), and carnitine (essential for oxidation of fat). Methionine is also a component of enkephalin and various endorphins (the painrelieving brain peptides), coenzyme A, heparin, biotin, and the tripeptide glutathione, an all-important antioxidant and detoxifying agent. Vitamin B_6, B_{12} and folate, and probably magnesium are involved in methionine metabolism; and selenium, an essential trace element, needs methionine for absorption, transportation and bioavailability (Chaitow,1985). With low methionine levels, folate is trapped in the liver causing temporary folic acid deficiency (Anonymous,2008). Methionine is metabolised to homocysteine, excess of which is believed to cause atherosclerosis by its oxidant effect (Murphy *et al*.,1985). This hazard is less with adequate Vitamin B_6 which helps reconversion of homocysteine to the antioxidant (cystathione). Methionine hastens histamine breakdown and reputedly lowers serum calcium in animals.

Methionine has been used to acidify urine, to antagonize radiation effects and to treat paracetamol poisoning

(Meredith *et al*.,1978) through its conversion into cysteine and glutathione. The average methionine dose is 1-2 g/day in 2 doses.

Methodology

Extraction of balanga mucilage

Crushed seeds were extracted by hot benzene in a large extraction flask, and after removal of the solvent by distillation; the crude fixed oil was left behind as a bottle green and somewhat opalescent liquid. It was treated with animal charcoal and Fuller's earth and was ultimately obtained as transparent light green oil(Mohammad Amini and Razavi, 2012).

Three different formulations were prepared which are as follows: Formulation-I was prepared according to the standard procedure without the incorporation of balanga mucilage. Formulation-II was prepared by adding 2 g of balanga mucilage. Formulation-III was prepared by adding 4 g of balanga mucilage. These three formulations were compared by conducting the evaluation tests for tablet dosage forms such as weight variation, hardness, friability, disintegration and dissolution tests.

Formulation

The conventional tablets were prepared with wet granulation technique. The active ingredients were mixed with the diluents for about 4-5 min.Granulating agent was prepared with soluble starch in the form of a paste. Granulation was done by mixing the mass powders to form a dough. Disintegrating agent as per the formula was dried starch and balanga mucilage. The mucilage was mixed along with the wet dough. The dough was made to pass through a sieve of number10. The above obtained granules were dried in the hot air oven for about 30 minutes at a temperature of 45 degrees. The above dried granules after removing the fines were lubricated with talc and aerosol. The above granules were punched into tablets using 10mm punch of concave surface (Table 1).

Evaluation tests as per I.P.

Hardness test

Monsanto hardness tester is used. The hardness of uncoated tablets should be between 3-7 kg/cm2 (Table 2).

Friability test

Roche friabilator is used. 20 tablets are selected at random and weighed. They are placed in a friabilator and operated for 100 revolutions at 25 rpm. The tablets are dropped at a distance of 6 inches with each revolution. The tablets are then dusted and reweighed. The acceptable limit is 0.5 to 1% (Table 3).

Disintegration test

The standard pharmacoepial disintegration apparatus is used. It consists of 6 glass tubes that are 3 inches long, open at the top and bottom is held against a 10 no. screen. Tablet is placed in each tube and the basket rack is positioned in a 1 liter beaker of water at 37 ^{0}C such that the tablet remains 2-5 cm below the surface of liquid on their upward movement and descend not closer than 2-5 cm from the bottom of the beaker. A standard motor device is used to move the basket assembly ontaining the basket up and down through distance of 5-6 cm at a frequency of 28-32 cycles/min. limit specified is 5-30 min. (Table 4).

Estimation of methionine in the pharmaceutical dosage forms by applying orthogonal polynomials

Methods

A novel method for the estimation of DL-Methionine in various pharmaceutical dosage forms like tablets and syrups was developed. The absorbance of the solution was measured at 570 nm. Beer-Lambert's law was observed to obey in the range of 10-100 µg. In the estimation of methionine in pharmaceutical dosage forms, the quadratic polynomial coefficient was computed by measuring the fluorescence of the drug in 0.01N hydrochloric acid and six points equally spaced at 5nm levels on the emission spectrum from 550 to 575 nm were plotted. The quadratic polynomial coefficient was found to be linear (directly proportional) to the concentration in the range 0.5 to 2.0µg.

Method - A

For quantitative analysis, mafenemic acid, dicyclomine, methionine suspension (20 mg) was transferred to 100 ml. calibrated flask and made up to the mark with water. In the case of tablets accurately weighed powder equivalent to 20 mg of methionine was transferred to 100 ml of calibrated flask and made up to the mark with water. Weigh accurately 20 mg of the reference standards and transferred into a 250 ml calibrated flask and make up to the mark with water. Filter the test reference standard solution, and pipette 5 ml of the test and reference standard into 25 ml calibrated flasks. The flasks are kept for 20 minutes in the boiling water along with the blank. The violet blue coloured chromogen having a maximum absorbance was recorded at 570 nm. The flasks were allowed to cool to room temperature before being made up to mark with water and the absorbance of the test and reference standard solutions were read against blank at 570 nm. (Table 5).

Method - B

The fluorescence readings of the standard methionine solution was scanned from 550 nm to 575 nm at 5 nm intervals, using 0.01N hydrochloric acid as blank. The excitation wavelength to measure the fluorescence reading was set at 570 nm as the excitation maxima occurred at this wavelength. The quadratic polynomial coefficient was calculated for six points of 5 nm intervals for every segment from 550 nm to 575 nm.

$$P2f=(5)F_{550}-(1)F_{555}-(4)F_{560}-(4)F_{565}(-1)F_{570}+(5)F_{575} \quad \ldots Eq\,1$$

Where F is the value of fluorescence and the subscript denotes the wavelength at which it is measured and the figures in the brackets taken from standard texts on numerical analysis. The quadratic polynomial coefficient (P2f) was more for the segment 550 to 575 nm and, hence, was chosen for the method (George,1968 and Rao,1966). The amount of drug content in the dosage form was calculated from equation 2.

$$Vt/Vs \times Ws/Wt \times A.W/D \times 100 = \%\ \text{of the label claim.} \quad \ldots Eq.\,2$$

Where Ws and Wt are the weights of the standard drug and the sample preparation.A.W is the average weight of the tablet and D the labeled drug content, all the weight being expressed in the mg. Vt and Vs are the values of quadratic polynomial coefficient, calculated for the test and standard, respectively, using Eq….active ingredients like asprin, Ibuprofen and excipients like mannitol, parabens, sugar. Essence and coloring agents did not interfere with proposed method as indicated by the quantitative recovery. The proposed method can be used for quantitative analysis of methionine in market formulations.

Results and Discussion

Chemical tests of *Lallemantia royleana* Benth

Balanga powder was subjected to ruthenium red test, gave reddish pink colour, indicating the presence of mucilage in the seeds. The above powder was also subjected to molisch test formation of reddish pink ring indicates the presence of carbohydrates.

Evaluation of physical properties of tablets

The hardness of tablets of all the three groups of formulations 1, 2, and 3. was measured and was found to be within the range of 5.0-6.2, 4.5-5.5,3.0-4.0, respectively. The addition of balanga mucilage appears to have reduced the bulk density of the powder blend and subsequently granules. However, the reduction in hardness for formulation 3 was found to be within the acceptable limits.

The three formulation categories were subjected to comparative studies, taking their friability into account. The friabilities of three formulations were found to be in the range of 0.48-0.88%,0.46-1.0%, and 0.97-1.2%, respectively. The increase in friability is attributed the proportionate increase in the content of balanga from formulations 1-3. However, the friability of formulation 3 is still within the acceptable limits. The three formulations were again subjected to disintegration test. The disintegrating times of the three formulations were found to be within the ranges of 5 min 50 sec,7.0 min, 3 min 50 sec,4min 50 sec.and 1 min 10 sec ,2 min 18 sec, respectively. The subsequent reduction in the disintegrating time is attributed again to the increase in the content of balanga. The disintegrant, particularly of mucilage's, swell in the presence of water and exert pressure on the granules to force them apart quickly.

Both isomers of methionine D and L forms, gave Rf values 0.32 and 0.40, respectively. The test sample showed the presence of both the isomers. The violet blue chromogen gave linear responses on the concentration range 10-100 mcg. The recovery experiments gave 98 to 99% recovery with 99 to 100% reproducibility by method A as shown in Table 5.

Also the formulation was put on trial for the estimation of percentage purity of methionine by applying orthogonal polynomials to all the three formulations. The formulation 1 was considered as the standard and the other two formulations were compared with that of the standard one. The quantitative analysis for methionine in the test formulations 2 and 3 showed that the foreign absorbance's were ignored by the application of the polynomial coefficients. The analysis was done by the application of quadratic polynomials with taking 6 points into consideration.

Conclusion

It is ascertained that natural disintegrants are far more superior to the synthetic ones. The disintegrant (balanga mucilage) is found to be absorbing water instantly, followed by its imbibition. This results in the easy break down of the tablets in turn resulting in the deaggregation of all the granules. Furthmore, mucilage of balanga seeds also helps in the dissolution of the drug. The high water absorption tendency of balanga mucilage which encircles each drug particle retains water within the vicinity and promotes the drug solvation. Balanga mucilage is found to be superior to other suitable disintegrants like aerosil (silica) in terms of action, availability *etc*. Aerosil has been found to be less preferable as a disintegrating agent because it has carcinogenic properties, it is highly expensive and furthermore it has very low density which creates difficulty in granulating tablets.The mucilage of balanga is, furthermore known to have various other properties like healing, laxative, *etc*. The mucilage is found to be stable and does not interact with other drugs or excipients. The above study needs to be conducted in much more elaborated way and has a lot of scope and potential in upgrading the formulations in drug industry. Also the method of estimating drug content by using orthogonal polynomials is much more feasible and reliable and is also precise.

Table 1: Fromulation of tablets with natural ingredients

S.No	Ingredients	Formulation-I for 200 tablets (Qty in g)	Formulation-II (a) for 100 tablets (Qty in g)	Formulation-II (b) for 100 tablets (Qty in g)
1	Mafenemic acid	60	30	30
2	Dicyclomine	40	20	20
3	dl-methionine	10	05	05
4	Starch	3.16	1.58	1.58
5	Starch paste	q.s	q.s	q.s
6	Lactose	q.s	q.s	q.s
7	Mannitol	q.s	q.s	q.s
8	Dicalcium phosphate	q.s	q.s	q.s
9	Talc	q.s	q.s	q.s
10	Dried starch	q.s	q.s	q.s
11	Aerosil	q.s	q.s	q.s
12	Balanga mucilage	Nil	**2 gms**	**4 gms**

Table 2: Hardness tests as per I.P

S. No.	Formulation-1 6(kg/cm2)	Formulation-2 (kg/cm2)	Formulation-3 (kg/cm2)
1	6	5.5	3
2	5.4	5	4
3	5	5.5	3.5
4	6.2	5	3
5	5.5	4.5	3

Table 3: Friability tests as per I.P

S. No.	Initialweight(W1)gm	FinalWeight(W2) gm	Friability= (W1-W2)/W1X 100
Formulation 1	12.51	12.40	0.88%
	12.38	12.30	0.64%
	12.52	12.42	0.79%
	12.40	12.33	0.56%
	12.45	12.39	0.48%
Formulation 2	12.85	12.75	0.95%
	12.90	12.79	0.85%
	12.85	12.79	0.46%
	12.86	12. 73	01.00%
	12.86	12.76	0.77%
Formulation 3	13.27	13.10	1.2%
	13.20	13.03	1.2%
	13.33	13.20	0.97%
	13.31	13.17	1.05%
	13.36	13.20	1.1%

Table 4: Disintegration tests as per I.P

S. No.	Formulation-I (time in min)	Formulation-II (a) (time in min)	Formulation-II (b) (time in min)
1.	7 min	4 min 10 sec	2 min 5 sec
2.	6 min	4 min 30 sec	1 min 50 sec
3.	6 min 20 sec	4 min 50 sec	1 min 40 sec
4.	7 min 10 sec	4 min 10 sec	2 min 3 sec
5.	5 min 50 sec	3 min 50 sec	1 min 10 sec
6.	6 min 2 sec	3 min 55 sec	2 min 18 sec

Table 5: Assay of methionine by the proposed method% amount found

S.No.	Method-I	Recovery studies	Reproducibility
Standard	98.9	98.8	99.1
Formulation-1	99.2	99.1	98.9

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