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Original Article

IN SILICO DOCKING STUDY OF HERBAL COMPOSITION AND DEVELOPMENT OF MOUTH DISSOLVING TABLETS FOR COMMON RESPIRATORY DISEASES THEREOF

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ABSTRACT

Objective: The present study aims to develop a novel mouth dissolving tablets containing a combination of herbal extracts and a bioactive constituent and evaluating it for activity against common respiratory diseases (*in silico* studies).

Methods: Docking study was done to provide a scientific foundation, keeping the traditional knowledge as a base. Four trial batches were developed. The final batch was then formulated and various pre and post-compression and assays were performed to evaluate the formation of good quality of product. The final batch was prepared by the method of direct compression and taken for accelerated stability studies.

Results: The final batch containing 10 % active ingredients, 7.5 % super-disintegrant and 47 % diluent was found to be stable, easily producible and economic.

Conclusion: This research work grasps possibilities for researchers in the development and evaluation of mouth-dissolving tablets with significant bioactive potential against common respiratory diseases.

Keywords: Accelerated stability study, Bioactive, Direct compression, Docking, *In silico* studies, Super-disintegrant

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INTRODUCTION

Respiratory diseases are wide spread and one of the major reasons of morbidity and mortality, predominantly in the developing world. These diseases are categorised as acute (pneumonia and influenza); chronic (chronic obstructive pulmonary disease (COPD) and asthma); occupational lung (byssinosis, asbestosis, and coal worker's pneumoconiosis); and other parenchymal lung diseases (immune-related lung diseases) [1]. Through decades, almost 4 million people die every year due to acute respiratory tract infections globally. Approximately 4.6 percentage people having moderate to severe COPD die every year. Children are the most affected population due to asthma, a common chronic disease affecting 14 % of children worldwide. Respiratory disorders contributes towards over all 10 % of disability-adjusted-life-years (DALY's), a matrix estimating the amount of dynamic and productive life loss [2-8].

Mouth dissolving tablets are a type of novel buccal cavity tablets that disintegrate and dissolve rapidly in the buccal cavity (saliva) and does not require chewing. They generally dissolve in 15 sec to 3 min in the buccal cavity and so mostly includes super-disintegrants and several taste masking agents [9-11]. These dosage forms are favourable for paediatric, geriatric or disabled persons facing problem in gulping tablets and capsules.

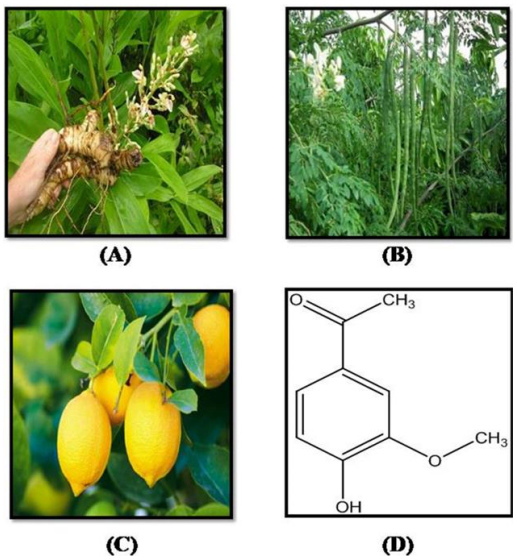

Fig. 1: Herbal components of formulation (A) *A. galanga* (B) *M. oleifera* (C) *C. limon* (D) Apocynin

Alpinia galanga (greater galangal or kulinjan) is traditionally used to treat asthma, bronchitis, heart diseases and rheumatism. It consists hydroquinone and hydroxymethylfurfural, galangoisoflavonoids, 1'-acetoxychavicol, galangin and galanganol B [12–16] (fig. 1A).1'-acetoxychavicol has a potential effect against asthma [15]. *Moringa oleifera* (drumstick tree or senjana) is widely used for anaemia, bronchitis, catarrh, chest congestion, asthma, cough, fever, respiratory disorders, TB and diabetes in the traditional system of medicine. It is a rich source of various vitamins, minerals, flavonoids such as niazirin and quercetin, and benzyl isothiocyanates [17-23] (fig. 1B). It treats the four basic symptoms of asthma i. e. dyspnoea, wheezing, chest tightness and cough [24]. *Citrus limon* (lemon or nimbu) is rich in vitamin C and flavonoids such as bergapten, eriocitrin, hesperidine and oxypeucedanin. Traditionally it is used to treat cold, cough, scurvy, sore throat and fever [25-29] (fig. 1C). Apocynin (4'-hydroxy-3'-methoxyacetophenone or acetovanillone) a naturally originating methoxy-substitute of catechol, is promisingly used for its bronchodilatory activity. It reduces influenza A virus induced lung inflammation and viral titres [30]. It is also reported to possess anti-arthritic, anti-asthmatic, anti-atherosclerotic and ant-oxidant activities [31-35] (fig. 1D).

Even in the present age of science and technology, the popularity of complementary and integrative therapies is on rise and people all over the world still opt for traditional systems of healthcare majorly due to less side effects, as compared to the modern allopathic medicines [36]. In the present work mouth dissolving tablets of dried extracts of *Alpinia galanga*, *Moringa oleifera*, *Citrus limon* and a bioactive apocynin were prepared and evaluated.

MATERIALS AND METHODS

Procurement of herbal extracts and bioactive

The dried plant extracts and the bioactive were procured form Bhagwati Herbal Pvt. ltd, Vapi, Gujarat and Sigma Aldrich, India, respectively. Percentage of phenolics and flavonoids are estimated in procured extracts.

Docking studies

Docking study was done using four different proteins against some of the common respiratory diseases i. e. influenza, asthma and COPD. The software used were Autodock Vina version 1.1.2 [37], MGL tools, Pymol and Open babel. The PDB IDs of the 4 different proteins used are 5EFA (influenza), 4FQH (influenza), 3WZE (asthma) and 3Q76 (COPD). The proteins were taken from RSCB PDB online and the ligands were obtained from PubChem. Protein and ligand were then prepared for docking using Autodock Vina. Grid box was formed around the appropriate receptor site and the docking was performed. The compatibility of ligand-protein interaction was visualized through the visualization software that is Pymol. The details of H-bond and Π-bond were then visualized using Autodock Vina.

Preliminary dosage form designing

Designing of the four trial batches was done at Sushen Medicamentos Pvt. ltd., Ahmedabad. Different batches were prepared with different concentration of extracts and excipients (table 1).

Table 1: Formulation of preliminary trial batches

S. No.	Ingredient	Quantity (g) Batch 1	Quantity (g) Batch 2	Quantity (g) Batch 3	Quantity (g) Batch 4
1	*A. galanga* extract	12	12	24	7.2
2	*M. oleifera* extract	12	12	24	7.2
3	*C. limon* extract	12	12	24	7.2
4	Avicel 102	108	185.1	108	108
5	*β*-cyclodextrin	-	87.5	-	-
6	Crospovidone	27	27	27	27
7	Sodium saccharin	3.6	7.2	3.6	3.6
8	Talc	7.2	3.6	7.2	7.2
9	Mannitol SD 200	164.6	-	128.55	179
10	Magnesium stearate	3.6	3.6	3.6	3.6
	Total	350	350	350	350

Formulation of the final batch

Tablets were prepared by direct compression method with a weight of 350 mg each. Formula of the same is given table 2. All the required ingredients were weighed as per the suggested quantities. Except that of talc and magnesium stearate which were sieved 60 # size separately, rest of the other ingredients were passed through 30 # sieve. All the ingredients except magnesium stearate were blended in the V-blender at 15 RPM for 10 min. Following this magnesium stearate was added in the same and mixed at 15 RPM for 5 min. This blend is used for the blend analysis and the tablets were compressed using Elisa press punching machine with 11 mm round punches at 10 RPM speed by means of B tooling. The tablets were packed and utilized for further evaluations.

Table 2: Formulation of the final batch

S. No.	Ingredient	% Taken	Quantity taken for 1 tablet (mg)	Quantity taken for 1000 tablets (gm)
1	Apocynin	1.43	5	5
2	*Alpinia galanga*	2.94	10.3	10.3
3	*Moringa oleifera*	2.94	10.3	10.3
4	*Citrus limon*	2.97	10.4	10.4
5	Avicel 102	30.86	108	108
6	Crospovidone	7.71	27	27
7	Sodium saccharine	1.03	3.6	3.6
8	Talc	2.06	7.2	7.2
9	Mannitol SD 200	46	161	161
10	Magnesium stearate	1.03	3.6	3.6
11	Orange flavour	1.03	3.6	3.6
Total		100	350	350

Evaluation of the tablets

The evaluation studies were done in 2 phases i. e., pre-compression evaluation and post-compression evaluation.

Pre-compression evaluation

This includes loss on drying and testing of flow properties of the powder mixture such as bulk density, tapped density, Carr's index, Hausner ratio, angle of repose, etc [38, 39].

Post-compression evaluation

It includes testing of appearance, weight variation, uniformity of weight, hardness test, friability test, disintegration test, wetting test, content assay, etc [38-41].

- Disintegration test-It is the time at which the tablet disintegrates. For mouth dissolving tablets the limit is 15 sec to 3 min.
- Wetting test-When a tablet is placed above the wet tissue, the time taken by water for travelling from the lower surface to the upper surface is known as wetting time. The limit for this test is from 10 sec to 1 min.
- Dispersion test-It is the time taken by the tablet to dissolve freely in 10 ml of water, which is passable to the narrowest sieve.

Stability studies

The aim of performing the stability parameters was to achieve a product which is stable and complies with safety and efficacy aspects as per regulations. The optimized formulation of mouth dissolving tablets was kept at room temperature condition 40̊ °C±2̊ °C and humidity 75 % RH±5 % RH for a period of three month [42]. The study was carried out at the end of 0, 1 mo, 3 mo and tested for disintegration time and hardness and assays were performed. The TLC fingerprinting was developed for mixture of extracts and bioactive as well as for the tablets of final batch using mobile phase, toluene: ethyl acetate: formic acid: acetone (5: 4: 1: 0.1, V/V).

RESULTS AND DISCUSSION

Analysis of the procured extracts

The phyto-chemical analysis of the extracts revealed presence of flavonoids, phenolic and saponins. Percentages of phenolic and flavonoid content in procured extracts are given in table 3.

Table 3: Assay of the procured extracts

S. No.	Extract	Flavonoid content (% w/w)	Phenolic content (% w/w)
1	*Alpinia galanga*	8.12±0.63 %	2.4±0.31 %
2	*Moringa oleifera*	10.53±0.22 %	2.23±0.12 %
3	*Citrus limon*	13.52±0.15 %	2.89±0.47 %

Docking study

Docking was done using four proteins targeting influenza, asthma and chronic obstructive pulmonary disorder (COPD) against various phytoconstituents of the above-mentioned plants and the bioactive. The docking score was found to be ranging from-10.5 kcal/mol (hesperidin of *C. limon* with 3WZE) to-3.9 kcal/mol (2-deoxy-d-ribose of *A. galanga* with 5EFA). Apocynin possess highest docking score of-9.0 kcal/mol with 4FQH and 3WZE. 1'-acetochavicol acetate from *A. galanga* possess maximum binding affinity of-6.2 with 3WZE. Binding energy of value of quercetin from *M. oleifera* is-8.4 with 4FQH and that of hesperidin from *C. limon* is-10.5 with 3WZE (table 4, fig. 2).

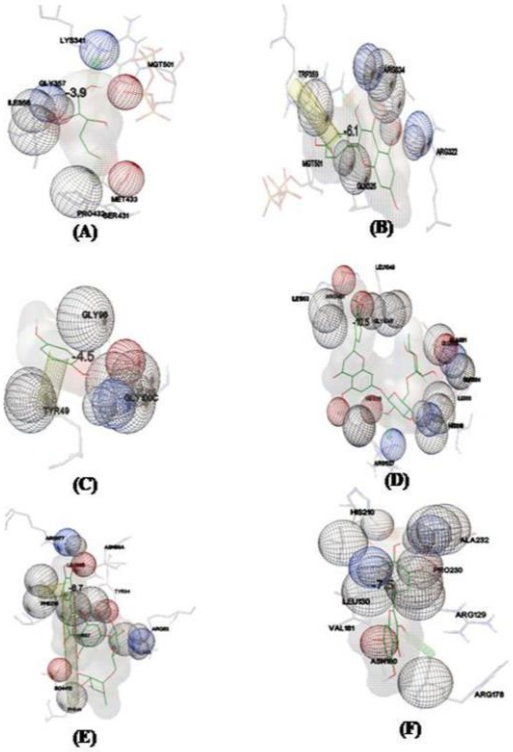

Fig. 2: Interaction diagram of protein with ligand, 5EFA with 2-deoxy-d-ribose (B) 5EFA with Kaempferol (C) 4FQH with Hydroquinone (D) 3WZE with Hesperidin (E) 3Q76 with eriocitrin (F) 3Q76 with quercetin

Table 4: Docking score of various phytoconstituents and bioactive

Plant/Bioactive	Phytoconstituent	Docking score			
		5EFA	4FQH	3WZE	3Q76
Apocynin	-	-6.9	-9.0	-9.0	-7.4
Alpinia galanga	Cinnamic acid	-4.9	-5.7	-6.1	-5.4
	Hydroquinone	-4.2	-4.5	-5.1	-5.0
	Hydroxymethylfurfural	-4.3	-5.3	-5.4	-4.8
	2-deoxy-d-ribose	-3.9	-4.3	-4.1	-4.5
	1'-acetoxychavicol acetate	-4.7	-5.7	-6.2	-5.5
Moringa oleifera	Kaempferol	-6.1	-7.7	-8.1	-6.4
	Myrecetin	-6.3	-8.3	-8.0	-7.0
	Niazirin	-5.3	-6.8	-6.8	-6.4
	Phthalic acid	-4.9	-5.6	-6.5	-5.2
	Quercetin	-6.4	-8.4	-8.1	-7.5
Citrus lemon	Ascorbic acid	-4.5	-5.6	-5.7	-5.5
	Bergapten	-5.2	-6.4	-6.5	-6.5
	Eriocitrin	-7.6	-9.4	-10.4	-8.7
	Hesperidin	-7.2	-9.8	-10.5	-8.8
	Oxypeucedanin	-5.9	-7.1	-7.4	-6.7

Preliminary batches

The formulated four trial batches were evaluated for pre and post-compression parameters and various assays were performed. The disintegration times of batch 1-4 are 35, 28, 75 and 30 sec, respectively (table 5-7). Batch 1 showed good flow properties, hardness and disintegration time over other batches, so selected for final batch preparation.

Table 5: Pre-compression evaluation of trial batches

S. No.	Parameter	Batch 1	Batch 2	Batch 3	Batch 4	Final batch
1	Bulk density (gm ml^{-1})	0.516	0.463	0.476	0.44	0.476
2	Tapped density (gm ml^{-1})	0.622	0.561	0.595	0.561	0.588
3	Carr's index	16.98	17.43	20.00	21.64	19.04
4	Hausner ratio	1.204	1.211	1.250	1.276	1.235
5	Angle of repose	25°	30°	35°	30°	20°
6	Loss on Drying	2.51	6.83	2.98	2.22	2.19

Table 6: Post-compression evaluation of trial batches

S. No.	Parameter	Batch 1	Batch 2	Batch 3	Batch 4	Final batch
1	Average weight (g)	3.512	3.482	3.505	3.532	3.499
2	Weight variation (mg)	351.32	349.56	350.83	353.63	349.87
3	Thickness (mm)	4.27	4.657	4.321	4.309	4.19
4	Diameter (mm)	10.92	10.89	10.93	10.92	10.95
5	Hardness (N)	78.6	93.5	80.6	96.5	89
6	Friability (%)	0.209	Nil	Nil	Nil	0.26
7	Wetting test (sec)	20	12	55	15	20
8	Dispersion test (sec)	12	10	42	11	20
9	Disintegration test (sec)	35	28	75	30	35

Table 7: Assay of trial batches

S. No.	Assay	Batch 1	Batch 2	Batch 3	Batch 4	Mixture of 3 extracts and bioactive	Final batch
1	Flavanoid content (% w/w)	16.43±0.28	16.02±0.32	22.32±0.31	7.61±0.41	20.42±0.24	19.94±0.28
2	Phenolic content (% w/w)	3.01±0.25	2.95±0.32	4.92±0.28	2.25±0.29	3.25±0.23	3.11±0.25

Table 8: Data of stability study

S. No.	Parameter	Limit	0 day	1 month	3 months
1	Appearance	Light brown colour	No change	No change	No change
2	Average weight	3.5 g	3.499 g	3.495 g	3.498 g
3	Shape	Round	No change	No change	No change
4	Hardness	80-90 N	89 N	88 N	89 N
5	Disintegration time	15 sec – 3 min	30-40 sec	30-35 sec	30-35 sec
6	Flavonoid content (% w/w)	-	19.94±0.38	18.93±0.26	18.43±0.42
7	Phenolic content (% w/w)	-	3.11±0.25	3.23±0.56	3.23±0.72

Formulation and evaluation of final batch

The formulated tablets were tested for pre and post-compression parameters and they passed all the tests significantly. The disintegration time of final batch was found 35 sec (table 5-7).

Stability studies

The tablets were found stable under the accelerated conditions 40° °C±2° °C and humidity 75 % RH±5 % RH for a period of three month as shown in table 8. TLC fingerprint of the mixture of extracts and

bioactive and that of tablets of final batch showed same resolution after three month also (fig. 3).

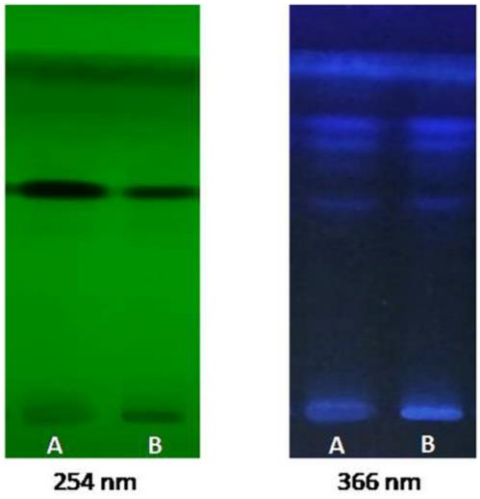

Fig. 3: TLC study A. Mixture of extracts and bioactive B. Final batch

CONCLUSION

The developed formulation was evaluated and the results indicated good flow properties, strength of hardness, disintegration, dispersion and wetting time. The final batch passed all the tests sufficiently. Thus, the proposed formulation is easily preparable, stable, economical and possesses a bronchodilatory effect.

The current research work will be supportive in developing efficacious and potent polyherbal formulations for the treatment of common respiratory diseases. This investigation can also be significantly used as an important tool for uncovering of possible mechanism for the development of herbal drugs, optimization and their evaluation for future researchers.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICTS OF INTERESTS

Declared none

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