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Formulation and Evaluation of Herbal Nutraceutical Tablets for Malnutrition

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The purpose of this study was to develop stable oral nutraceutical tablets containing herbs with high nutritive value like Mushroom, Amalaki and Ashwagandha in whole powder form. Simple direct compression technique was used for formulation of immediate release tablets. Effect of various directly compressible diluents like microcrystalline cellulose, dicalcium phosphate anhydrous and mannitol was explored. Final selection of formulation was done based on evaluation of batches for various pre-compression and post-compression parameters. Herbal ingredients are susceptible to degradation in presence of moisture and hence moisture protective coating was given to optimized batch of tablets that would improve their stability and shelf life.

Keywords: Malnutrition, immediate release tablets, direct compression

Introduction:

Malnutrition occurs when human body does not get enough nutrients like protein, fat, carbohydrates, vitamins and minerals to maintain health. This in turn causes weakness and other health problems affecting immunity. Treatment for malnutrition, in general, includes increasing nutrients in diet and administration of supplements that will enhance immune function. For this, natural sources may be utilized which are recommended in traditional systems of medicine as tonic, devoid of side effects and also available at low cost.

Amalaki and Ashwagandha are recommended in Ayurveda for their variety of therapeutic uses. Amalaki is a tonic, rich source of vitamin C that detoxifies the body and increases total protein levels due to its ability to create a positive nitrogen balance. It promotes longetivity[1]. Ashwagandha is rejuvenating and used to treat general debility and depressed immunity[2]. Mushroom is recommended in Chinese medicine for restoring body's health, balance and natural resistance to disease. It is high in vegetable proteins, iron, fiber, vitamins & minerals.

Formulation of whole powders of these herbs in the form of conventional immediate release tablet would ensure maximum benefit from all nutritive constituents present in herbs, ease of administration, better acceptance than churna, prolonged shelf life and quality assurance.

Various tabletting techniques can be used to formulate immediate release tablets. Direct compression technique by which tablets are compressed directly from mixtures of active and excipients was used for formulation [3]. Direct compression does not require use of water or heat during formulation and is thus ideal for moisture sensitive herbal actives. Excipient selection was based on suitability to direct compression process. Formulation optimization was done by comparing various parameters such as flowability, compressibility of powder blend and *in-vitro* disintegration and dissolution of tablet batches. The optimized tablet batch was coated with moisture protective coating.

Methods and Materials

Materials:

Powders of amalaki and ashwagandha were purchased from Bharat Vanaushadhi, Maharashtra, India. Commercially cultivated variety of mushroom powder was purchased from National Mushrooms, India. Ludiflash, Kollidon CL-SF were obtained as gift sample from BASF, India; Pearlitol200SD, Avicel PH 102 (MCC) was obtained as gift sample from Signet, India; Dicalcium phosphate anhydrous (DCP) was obtained from Uma brothers, Maharashtra, India; Aerosil 200 and magnesium stearate were purchased from CDH Laboratories, India.

Method:

Formulation Design

Tablets containing 60% w/w active mixture of mushroom, amalaki and ashwagandha powders (3:1:1) were prepared by direct compression technique. Active as well as excipients were passed through 60 mesh sieve and weighed as per the quantities specified in table 1. Active was blended with directly compressible diluents like MCC, DCP, Mannitol (Pearlitol) and co-processed mannitol (Ludiflash). Crospovidone (Kollidon CL-SF) was used as superdisintegrant. The final powder blend was lubricated with 1% magnesium stearate and 1% aerosil 200 was added as glidant.

Table 1: Composition ($\%^{w}/_{w}$) of immediate release herbal tablet batches L1-L13

Ingredient	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13
Active	60	60	60	60	60	60	60	60	60	60	60	60	60
Avicel PH102	38	19	19	19	-	-	-	-	36	18	18	19	-
DCP	-	19	-	-	-	36	-	18	-	18	-	-	-
Pearlitol	-		19	-	-	-	36	18	-	-	18	-	-
Ludiflash	-	-	-	19	38	-	-	-	-	-	-	18	37
Kollidon CL-SF	-	-	-	-	-	2	2	2	2	2	2	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1	1

Powder blend was compressed to 600mg tablets on single punch tablet machine using 12.5 mm round die and punch set with appropriate compression pressure.

Evaluation of powder blend

Powder blend was evaluated for the following pre-compression parameters. The results are given in table 2

Angle of repose was measured by fixed funnel and cone method. Powder was allowed to flow through a funnel until the apex of conical pile just touches the tip of the funnel. Angle of repose is maximum angle between the surface of a pile of powder and horizontal plane, when powders are allowed to flow freely from a certain height and was calculated using formula.
$\theta = \tan^{-1} h/r$ Where, θ is angle of repose, h is height of pile and r is the radius of the base pile.

Bulk Density (ρ_b) was determined by pouring blend into a graduated cylinder. Bulk volume (V_b) and weight of powder (M) was determined. Bulk density was calculated using the formula: $\rho_b = M/V_b$

Tapped Density (ρ_t) was determined by tapping the measuring cylinder containing known mass of blend for a fixed time. The minimum volume (V_t) occupied in the cylinder and weight (M) of the blend was measured. Tapped density (ρ_t) was calculated using the formula: $\rho_t = M/V_t$

Carr's compressibility index was calculated by using the formula: $I = \{(V_o - V_t)/ V_o\} X 100$

Hausner ratio was calculated by using the formula: ρ_t/ρ_b

Where ρt is tapped density and ρb is bulk density. Lower Hausner ratio (< 1.25) indicate better flow properties than higher ones (>1.25).

Table 2: Evaluation of pre-compression parameters

Parameters	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13
Bulk density (g/cm³)	0.471	0.482	0.475	0.478	0.487	0.491	0.476	0.485	0.472	0.479	0.480	0.485	0.489
Tap density (g/cm³)	0.585	0.583	0.581	0.565	0.582	0.586	0.588	0.575	0.579	0.576	0.583	0.572	0.587
Carr's Index (%)	19.48	17.32	18.24	15.39	16.32	16.21	19.04	15.65	18.48	16.84	17.66	15.21	16.69
Hausner's ratio	1.242	1.209	1.223	1.182	1.195	1.193	1.235	1.185	1.226	1.202	1.214	1.180	1.2
Angle of Repose (°)	38.56	37.56	38.14	33.80	35.86	35.52	39.17	34.75	38.46	36.38	37.83	33.68	36.06
Flowability	Fair	Fair	Fair	Good	Good	Good	Fair	Good	Fair	Fair	Fair	Good	Fair

Evaluation of tablets

Tablets were evaluated for the following post-compression parameters. The results are given in table 3

Weight variation test: Twenty tablets were selected at random and their average weight was determined using an electronic balance. The tablets were weighed individually and compared with average weight.

Hardness of tablets was determined individually with the Monsanto hardness tester.

Friability of pre-weighed ten tablets was determined by using Roche friabilitor at 25rpm for 4 min. The tablets were dedusted and reweighed.

%Friability = (Loss in weight/Initial weight) x 100

In-vitro **disintegration time:** Disintegration test was performed using a USP disintegration apparatus, with 900ml distilled water at 37±2°C. Time required for complete disintegration of six tablets was recorded.

Assay of active content: was carried out in terms of polyphenol content which was found to be common and high in all the three herbs through Folin Ciocalteau assay[4] and can be correlated with antioxidant activity to boost immune system in malnutrition.

Ten tablets were powdered and a sample of 1.2g of tablet powder was weighed and extracted with 100 ml of distilled water on an ultrasonic bath for 20 min. The extract was centrifuged for 5 min. at 14000 rpm. Supernatant 5ml was diluted to 50ml and 1ml of this solution was mixed with 5 mL of Folin-Ciocalteu Reagent (diluted 10 fold with distilled water) and 4ml of 1M sodium carbonate solution. Mixtures were shaken and allowed to stand for 30 min in dark at room temperature. Absorbance was measured at 765 nm using spectrophotometer. Blank consisted of 5 mL Folin-Ciocalteu reagent, 1 mL distilled water and 4 mL sodium carbonate solution. The amount of polyphenol was calculated as gallic acid equivalent $\%^{w}/_{w}$ using standard curve equation, y = 0.005x + 0.054, r^2= 0.992.

Table 3: Evaluation of post-compression parameters

Parameters	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13
Hardness (kg/cm2)	6.5	6.0	5.0	5.5	5.0	4.0	4.0	4.5	6.0	5.5	4.5	5.5	4.5
Friability (%)	0.31	0.35	0.52	0.38	0.55	0.76	0.65	0.64	0.35	0.41	0.55	0.43	0.58
Disintegration time (min)	20.15 ±0.132	14.33 ±0.159	12.75 ±0.172	5.46 ±0.124	5.36 ±0.133	7.13 ±0.104	5.91 ±0.131	6.7 ±0.112	8.66 ±0.122	8.35 ±0.109	9.41 ±0.136	4.7 ±0.148	4.46 ±0.128
Assay (%)	97.681	98.214	99.393	97.432	98.465	98.135	99.448	97.190	97.536	98.632	97.229	99.658	98.212
Average weight (mg)	600 ±1.31	598.42 ±1.56	599.34 ±1.206	600.04 ±1.08	597.43 ±1.12	600.23 ±1.22	601.00 ±1.82	598.32 ±1.72	600.20 ±1.41	601.33 ±1.36	600.78 ±1.08	600 ±1.98	599.26 ±1.76

In-vitro dissolution test:

The release of polyphenol from conventional immediate release tablets was determined using USP dissolution test apparatus Type 2 at 50 rpm. Dissolution was examined in 900ml of distilled water with two tablets placed in each of 6 dissolution vessels. The temperature was maintained at 37 ± 0.2°C. Samples each of 10 ml were withdrawn at 10, 20, 30, 40, 50 and 60 min time interval, filtered through wattman filter paper and replaced with an equal amount of fresh dissolution medium. Equal volumes of the filtered specimens withdrawn were combined and used as the pooled sample, as test solution[5, 6]. Test solution was analyzed for polyphenol content by Folin Ciocalteau assay. The amount of total polyphenols dissolved was calculated from the calibration curve of gallic acid. The % release per tablet was reported. The results are given in table 4 and figure 1.

The *in-vitro* dissolution study was carried out with respect to total polyphenol contents present in herbal actives. This non-specific dissolution was intended to be diagnostic of batch-to-batch variation. The operative assumption inherent in this procedure was that if the polyphenols are demonstrated to have dissolved within time frame and under specified conditions the tablets do not suffer from formulation related problem.

Table 4: Dissolution profiles of all formulations

Time (min)	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13
0	0	0	0	0	0	0	0	0	0	0	0	0
10	21.19	30.46	49.26	56.18	40.06	52.59	43.29	33.16	32.12	50.44	71.77	60.3
20	42.36	59.36	67.55	68.28	67.20	78.32	75.03	60.98	51.89	74.12	93.15	82.52
30	71.28	82.52	90.16	85.32	81.6	84.21	85.25	85.44	68.33	87.24	97.96	89.95
40	83.39	91.23	92.53	91.33	88.72	95.23	97.54	97.31	90.71	95.53	98.22	97.39

50	90.77	93.56	94.41	95.59	93.32	97.27	97.26	92.42	92.34	96.31	98.73	97.41
60	93.17	95.78	96.57	96.41	94.29	97.82	97.56	93.75	94.77	98.17	99.41	98.15

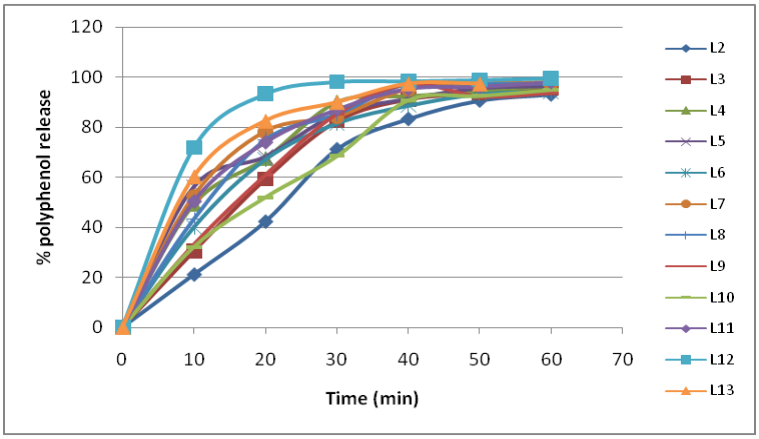

Figure1: In-vitro dissolution profile of formulations

Coating of tablets

Most of the active herbal ingredients are hygroscopic in nature and tend to pick moisture from atmosphere when exposed to high humidity. Such moisture pickup deteriorates the product through chemical degradation and microbial or fungal growth. Moisture barrier film coat of **Kollicoat Protect** was thus applied to optimized batch L12 of compressed tablets and coated tablets were evaluated. The details of coating are given in table 5 and the results of evaluation of coated tablets are presented in table 6

Table 5: Coating parameters

Coating product	Kollicoat Protect (barrier, TM; PVA-PEG + PVA)
Coating system	Aqueous
Color	White
Colorant	Titanium dioxide
Inlet air temperature	50°C ±2°C
Tablet bed temperature	40°C ±2°C
Spray rate per minute	4 gm/min.
Solvent system	Aqueous
Total weight of tablet before coating	260gms
Total weight of tablet after coating	268gms
% weight gain	3.07 %

Table 6: Evaluation of coated tablet

Sr. No.	Test	Result
1	Assay (%)	98.523
2	Average weight (mg)	618.5±1.52
3	Hardness (kg/cm2)	6.0
4	Friability (%)	0%
5	Disintegration time (min)	6.3±0.26

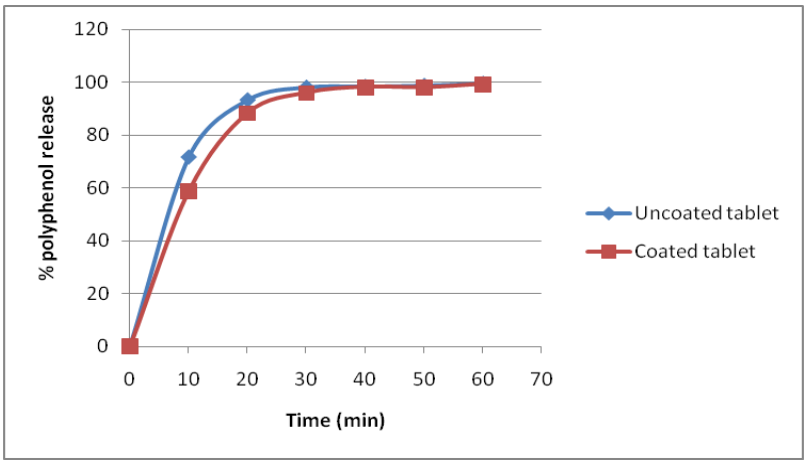

Figure 2: *In-vitro* dissolution profiles of uncoated and coated tablets

Results and Discussion

Direct compression method was used for formulation of immediate release nutraceutical tablets which minimized processing steps and eliminated wetting and drying process that show detrimental effects on herbal actives.

The tablet formulation consisted of the active, fillers, disintegrants, lubricant and glidant. Powder intended for compression into tablets must possess good compressibility and fluidity. Problem in fluidity cause variation in die filling and consequently variation in tablet weight and strength. Hence excipient selection was done by considering these attributes and only directly compressible grades of fillers having acceptable flow properties were taken for the study.

Pre-optimized concentration of 1% $^{w}/_{w}$ magnesium stearate as lubricant and aerosil as glidant was added to the powder blend to avoid tablet defects like picking and capping and improve its flowability from hopper to die.

Diluents selected were microcrystalline cellulose, dicalcium phosphate anhydrous and mannitol. Two different forms of mannitol were used; spray dried form 'Pearlitol 200SD' and co-processed form 'Ludiflash'. Total thirteen batches were prepared with formulations containing Avicel PH102, Dicalcium phosphate anhydrous, Pearlitol 200SD and Ludiflash as diluents used alone and in combination (table 1). All the batches of tablets were produced under similar conditions to avoid processing variables.

Powder blend evaluation studies revealed that batches L5 and L6 containing Ludiflash and dicalcium phosphate, respectively as single diluent possessed better flow properties as compared to batches L1 and L7 containing Avicel PH102 and Pearlitol 200SD, respectively. However, considering all the formulations, the combination batches of Avicel PH 102 and Ludiflash (L4 and L12) possessed the best flowability (Table 2).

Kollidon CL-SF which is chemically crospovidone was selected as the disintegrant. About 2-5 % concentration of this superdisintegrant is generally recommended in tablets prepared by direct compression. However in the present study the concentration from 1-2% was found to be

sufficient to keep the disintegration time of tablets below 15min. Tablet batches L2 and L3 containing Avicel PH 102 disintegrated within 15 min even without the presence of superdisintegrant which can be attributed to disintegrant action of microcrystalline cellulose through dual mechanism of wicking and swelling [7]. However this was not observed in case of batch L1 containing Avicel in concentration of 38% and disintegration time was 20 min. Lower disintegration time exhibited by batches L4, L5, L12 and L13 can be explained by the presence of intragranular disintegrant within the diluent Ludiflash.

The results found for hardness and friability tests in this study were remarkably related. Tablet formulations presenting lower hardness values also had higher friability values (table 3). Hardness was influenced by the type of diluent and presence of superdisintegrant. Tablet batches L1 and L9 containing Avicel PH-102 showed higher values of hardness. This may be due to excellent compressibility of microcrystalline cellulose which adds compact and strength into the tablets. Tablets from batch L5 and L13 containing Ludiflash as diluent were harder than batch L7 containing Pearlitol 200SD although both are mannitol excipients. This may be the effect of co-processing of mannitol with Poly vinyl acetate copolymer which is a binder. Mechanical strength of tablets containing Ludiflash was further increased when it was combined with Avicel PH102. This can be observed from comparison of batches L4 and L12 with batches L5 and L13, respectively.

Tablets of batch L6, L8 and L9 showed rough surface texture which may be due to the abrasive nature of dicalcium phosphate anhydrous [8].

Tablet batches containing superdisintegrant showed lower hardness and higher friability as compared to batches with same diluents but without superdisintegrant. However friability was below 1% limit for all the batches.

In vitro dissolution studies of the prepared immediate release tablets were performed in distilled water using USP dissolution apparatus type 2. All the batches except batch L2 showed polyphenol release above 80% at the end of 30 minutes. Batches with mannitol excipient showed higher % release at the end of the study as compared to batches L2, L6, L9 and L10 without any of the mannitol excipients. Batch L12 showed release above 90% at 20min and highest release amongst all batches at the end of 1hr. (table 4 and figure1)

Average % assay of the prepared tablets ranged from 97.190 to 99.658. Polyphenols constitute a major chemical entity in all three herbs mushroom, amalaki and ashwagandha. Hence, the developed formulations were evaluated with respect to total polyphenol content.

Batch L12 was thus found to be the best batch with respect to both pre and post compression parameters. Moisture barrier coating was applied to tablets from batch L12 to protect the moisture sensitive herbal ingredients in tablet core. Application of moisture barrier coating resulted in slight increase in tablet hardness and *in-vitro* disintegration time. However, coating showed little effect on dissolution of tablet core (figure 2)

Conclusion

Conventional uncoated and coated stable immediate release tablets containing nutraceutical herbs mushroom, amalaki and ashwagandha useful in undernutrition were successfully formulated. From the research work it is concluded that herbal nutraceutical powders can be prepared in the

form of cost effective tablet formulations to improve their stability, consumer compliance and acceptability.

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