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Formulation Development, Optimization and *In-Vitro* Evaluation of Ginger Root Extract (5%w/w 6-Gingerol) 300mg Timed Release Veggie Capsules.

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ABSTRACT

The major objective of any dosage form development is to ensure the delivery of specific and reproducible amounts of pharmacologically active compounds to the body in the maximum amount possible. Today's most frequently used dosage forms are orally administered solids formulated such as tablets, capsules or powders. Timed-release products intend to improve delivery efficacy and/or effectiveness; for instance, the frequency of dosing can be reduced and, in certain cases, the actual daily dose can be reduced, offering the manufacturer a financial benefit. There have been many techniques developed for producing the variety of timed-release products. Ginger is a natural drug, which is used for nausea and vomiting, to treat bleeding disorders and rheumatism. In conventional dose is thrice a day, 8-10 gm which is not at all convenient for the patient. Increase the patient compliance is also a great challenge which is continuously improving by the novel drug delivery system. The main objective of the present work is to design Ginger root extract powder (5%w/w of 6-gingerol) timed release dosage form of the drug with the help of a novel clear transparent veggie capsule shell of '0' size made up of cellulose and natural substance. The objective in formulating a sustained release dosage form is to be able to provide a similar blood plasma level pattern for up to desired hrs (12hrs) after oral administration of the drug. The formulation, optimization, destructive quantification parameters and *in-vitro* studies of the drug have focused in this research article. The presented work sought a futuristic research for the benefit of the patients.

Keywords: Sustained Release, Timed drug delivery, Novel drug delivery, Veggie Capsules

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INTRODUCTION

Timed release capsules are sustained release dosage forms which engineered by using various types and layers of coating around the active substances, which dissolve at various times and areas of the body[1].The first significant marketed sustained release dosage forms were encapsulated mixed slow release beads, to which was applied the barrier principle of controlling drug release. In these systems, the drug is distributed onto beads, pellets, granules or other particulate systems using conventional pan coating or air suspension coating, a solution of the drug substance is placed on small inert non-pareil seeds or beads made of sugar or on microcrystalline cellulose spheres. The non-pareil seeds are most often in the range of 425 nm to 850 nm, whereas the microcrystalline cellulose spheres range from 170-600 nm. The microcrystalline cellulose spheres are considered as more durable during production than sugar based cores. If the dose of the drug is large, then the starting granules of material may be composed of the drug itself. Some of these granules may remain uncoated to provide immediate drug release. Other granules in about three-fourth receive varying coats of lipid material like beeswax, carnauba wax, glycerol monostearates or cetyl alcohol or a cellulosic material like ethyl cellulose. Then granules of different coating thicknesses are blended to achieve a mix having the desired drug release characteristics in the gastro intestinal tract[2].

Timed-Release Formulation[3]:

Timed-release products intend to improve delivery efficacy and/or effectiveness; for instance, the frequency of dosing can be reduced and, in certain cases, the actual daily dose can be reduced, offering the manufacturer a financial benefit. A variety of techniques have been used to prepare oral time-release delivery systems, and combining them is often done to maximize their advantages. One of the goals behind developing time-release products was to maintain a steady level of drug concentration in the blood. A time-release product essentially controls the rate at which a compound is available for absorption. In doing so a balance can be achieved between the amount absorbed and that being excreted. This balance can smooth the peaks and valleys (fluctuations) of the concentration of the drug in the blood, maintaining a steady level. This significantly improves the product's efficacy since the effective concentration range that a compound needs to be at any given time can be maintained. An effective range (therapeutic or pharmacological window) is determined by the body's tolerance for the compound of interest. Going over the high end of this range, one may experience toxic effects while concentrations below the lower end of the range render the product ineffective. This is achieved by most time-

release delivery systems that release small amounts of active at frequent intervals. Orally administered time-release delivery systems are preferred because they offer flexibility in dosage-form design and are relatively safe in-spite of the difficulties of releasing drug due to the variable gastrointestinal environment.

Timed release dosage form is not preferred[4]:

- If the active compound has a long half-life (over 6 hr), it is sustained on its own.
- If the pharmacological activity of the active is not related to its blood levels, time releasing then has no purpose.
- If the absorption of the drug involves an active transport, the development of a time-release product may be problematic.
- If the drug has a short half-life, it would require a large amount to maintain a prolonged effective dose.

Beyond these considerations, there are certain limitations associated with time-release product development. The most, one can hope for an oral time-release delivery system is 12 hr due to its effective transit in the gastrointestinal tract. There is a significant time span recognition between desired activity and adverse effect. Poor formulation design could result in dose dumping or poor dispersion of the drug, creating a reservoir effect that could allow large concentrations of the active to come in contact with the GI mucous and enhance local toxic effects of a potentially irritant active. Reduction of absorption rate to reduce side effects of actives might result in reduced absorption. Inappropriate dosing intervals that result in a significant residual amount of active in relation to the dose could push the steady level into the toxic range. There have been many techniques developed for producing the variety of timed-release products. Based on such techniques, time-release products can be categorized in four groups[5].

- Repeat Action
- Controlled Release
- Delayed Release
- Sustained Release

The goal in designing sustained or controlled delivery systems is to reduce the site of action, reducing the dose required, or providing uniform drug delivery (Figure 1)[6].

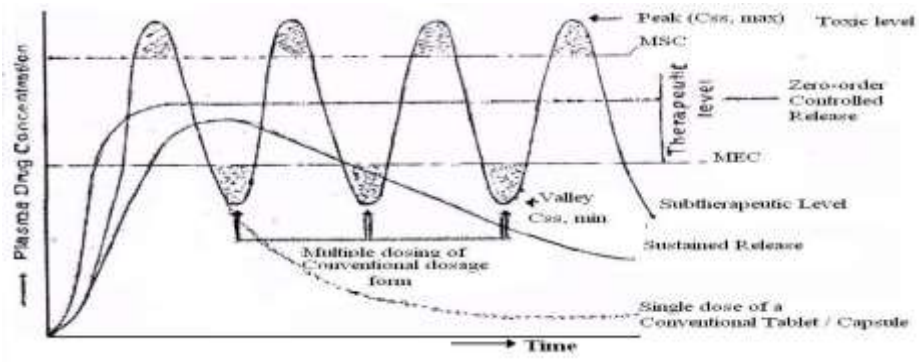


Figure 1: Plasma drug concentration –time profile

If one were to imagine the ideal drug delivery systems, two pre requisites would be required. First it would be a single dose for duration of treatment whether it be for days or weeks as Hypertension or Diabetes. Secondly, it should deliver the active entry (drug) directly to the site of action, thereby minimizing to eliminating side effects. This may necessity at delivery to specific receptors, or localization to cells or to specific areas of the body[7].

Encapsulated slow release granules:

The mode of release delivers the drug continuously slowly the release profiles can follow first order kinetics, meaning upon on set the release rate is fast and then slows down with time. The first significant marketed sustained release dosage forms were encapsulated mixed slow release beads, to which was applied the barrier principle of controlling drug release A typical mix consists of uncoated pellets providing the loading dose and pellets are designed to release drug at 2 or 3 hr, 4 or 6 hr and 6 or 9 hr. The key factor controlling drug release is moisture permeation of the barrier, which depends on coating thickness. In the case of high milligram potency formulations individual crystals of drug of palletized drug may be coated by pan or fluidized bed process with a retardant barrier combinations of waxes, fatty acids and esters can be applied using fluidized-bed technology[8]. New technological advances have brought many innovative drug delivery systems to the market and others to the brink of commercialization. A variety of approaches have been investigated for the controlled release of drugs and their targeting to selective sites. Synthetic and naturally occurring absorbable polymers in the form of matrix (monolithic) devices, hydro gels, micro spheres etc. finding increasing using drug delivery system[9].Naturally occurring polymers have some inherent drawbacks such as, poor dimensional stability due to swelling in- vivo, poor in-vivo mechanical strength. And low elasticity, possible occurrence of antigenic response, tissue irritation due to residual aldehyde cross linking agents and variability in drug release kinetics therefore a synthetic polymer is considered a good choice for the controlled drug delivery systems.

Among the synthetic polymers available in the market the most extensively studied polymers are the derivatives of cellulose ethers[10-12].

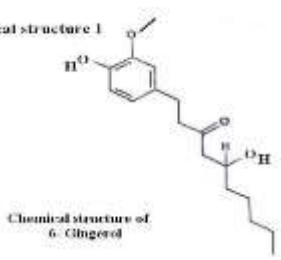
The drug profile[13-16]*:*

Drug Name: Ginger Root Extract (5% w/w 6-gingerol) powder.

Synonyms: Gingerin

Fig. 3

Chemical structure 1



Chemical structure of 6- Gingerol

Chemical Structure:

Chief Chemical Constituent: 6-Gingerol.

Biological Source: Crude dried extract obtained from the natural source of Ginger rhizomes i.e *Zingiber officinale; Roscoe,* belongs to family Zingiberaceae, Containing 5%w/v of 6-gingerol. Gingerin is the oleoresin obtained by the method of percolation of the powdered rhizomes.

Appearance: Yellowish brown coloured powder, has a characteristic aromatic odour and a spicy and burning taste.

Flowability: Free flowing power.

Storage: In cool and dry place.

Shelf life: 3 years when properly stored.

Category: Nutritional Supplement.

Action: Digestive-aid and anti-nausetic remedy.

Indications: Nausea, Vomiting, Rheumatoid arthritis and bleeding disorder.

Adverse Reaction: Heart burn. Epigastric pain, Tenderness. Diarrhoea.Dyspepsia, Constipation, Abdominal pain, Palpitations, Drowsiness. Skin reaction, Headache.

Dosage: 300 mg t.i.d.

Objective of the study:

Ginger is a nutrient, which is used for nausea and vomiting. It is a phenolic compound that is an important pre-cursor in the bio-chemical synthesis of cholesterol and to treat bleeding disorders and rheumatism. In conventional dosage, it has to take thrice a day i.e., 8-10 gm for the treatment of nausea and vomiting. The dose is more for ginger. This much big tablet thrice a day is not at all convenient for the patient to take. Now a day's, increase the patient compliance is also a great

challenge for the pharmacist, which is continuously improving by the novel drug delivery system. The main objective of the present work is to formulate time release dosage form of the drug. The objective in formulating a sustained release dosage form is to be able to provide a similar blood level pattern for up to desired hrs after oral administration of the drug. So this work has been to taken to make a sustained release dosage form of the ginger to decrease the dose frequency as well as to increase the patient compliance.

MATERIALS AND METHOD

Materials used:

Drug: Ginger Root Extract (5%w/w) powder:- Coastal Laboratories, Andhra Pradesh. 100gm received as an ex-gratis sample.

Preparation of stock solution[17]

0.1N Sodium Hydroxide: Potassium hydrogen phthalate previously powdered & dried at 120˚C for 2 hr & dissolve in 75 ml of CO_2 free water. Add 0.l ml of phenolphthalein solution and titrate with the sodium hydroxide solution until a permanent pink colour is produced. Each ml of 0.1 M NaOH is equivalent to 0.02042 g of $C_8H_5 KO_4$.

Thymol blue: Dissolve 0.l g of thymol blue in 100 ml of ethanol (95%) & filter, if necessary.

Phenolphthalein: Dissolve 0.l g of phenolphthalein in 80 ml of ethanol (95%) and add sufficient water to produce 100 ml.

Preparation of drug - polymer granules[18]

Dry mixing:

Required quantity of Ginger root extract (5%) powder and dibasic calcium phosphate was taken into shifter of mesh size 30#.Then mix these two in a polybag mixing.

Preparation of binder solution:

Required quantity of polyvinyl pyrrolidone was added with the 1:1 preparation of water and isopropyl alcohol in a beaker under stirring condition.

Preparation of granules:

Granules were prepared by wet granulation method. Wet mass was prepared by the mixing the binder solution with the dry mix. Passed through sieve no 16 and dry it in hot air chamber at 40°C and moisture content of granules was determined till the moisture content was less than 1%. After drying, separate the fines by sieve no 30. Then repeat the process to get all granules of size sieve no 16 to sieve no 30.

Preparation of coating solution:

The coating solution of ethyl cellulose and hydroxy propyl methyl cellulose (k4 m) was prepared separately in IsopropyI alcohol and Methylene chloride mixture (1:2) at different concentration by stirring in a magnetic stirrer.

Granules Evaluation[19]:

Granules are evaluated for physico-chemical characteristics like angle of repose (flow properties), bulk density and drug- content estimation.

(a) Angle of Repose:

Flow properties of powders are important in the manufacture of capsules. Because non-uniform flow will result in variation in weight of the tablets, which in turn affects the dose of the drug per capsule, it also creates problem of hardness during compression of tablets. It was measured by the fixed funnel method using the procedure as follows: A glass funnel with a stem of 15-20 cm was selected and fixed to the funnel stand, a graph paper was placed on table. Granules were allowed to flow to form a heap. The circumference of the heap was marked and measured the height of the pile using two rulers. The height was measured and noted as (h). The area (πr^2) was determined, radius(r) was calculated and substituted in the formula to obtain the angle of repose ($\theta = \tan^{-1} h/r$). Repeated this experiments twice more and calculate the average angle of repose.

(b) Bulk density: Bulk density of granules influence porosity, hardness of tablets and disintegration of tablets and also can be used to check the uniformity of granules from batch to batch. It is determined by using bulk density apparatus.

Determination of bulk density[20]:

Fill the measuring cylinder of the bulk density apparatus with the granules by tiring the weight of the measuring cylinder. Note down the weight of the granules which is equivalent to the volume of 100 cc. The knob was adjusted for 100 tapings. Note the final volume as tapped volume.

Bulk density is calculated by using formula.

True density= weight of granules (gm)/untapped volume of granules (cc). Bulk density= weight of granules (gm)/ tapped volume of granules (cc).

Filling of capsules[21]:

After coating of granules with different % of Ethyl Cellulose and Hydroxy Propyl Methyl Cellulose granules were blended properly and filled in capsules with hand filling machine. Clear transparent hard veggie '0' size capsules prepared from cellulose were used for filling. The two different formulations of capsules are shown below in Tables 1.

Table 1: Formulae for Timed release capsule (Fl &F2)

Ingredients	Formula for each capsule (in mg) F1	Formula for each capsule (in mg) F2
Ginger Root Extract Powder (5%)	300	300
Di-Calcium Phosphate (DCP)	5	6
Poly vinyl Pyrrolidone (PVPK-30)	20	18
Ethyl Cellulose	60	64
Hydroxy Propyl Methyl Cellulose	10	12
IsoPropyl Alcohol	q.s	q.s
Methylene Chloride	q.s	q.s
Colour /Dye	q.s	q.s

Evaluation of capsules[22]

The capsules were evaluated for the following parameters,

- General appearance. Colour, Odour, Taste, Shape.
- Diameter.
- Drug content uniformity.
- Weight variation test.
- In- vitro dissolution studies.

General appearance

Five capsules from both batches were randomly selected and organoleptic properties such as colour, odour, taste, shape, were evaluated.

Weight variation test[23].

Weighed 20 capsules selected at random and calculated the average weight. Then percentage deviation from the average was calculated. According to IP standards, not more than two of the individual weight deviates from the average weight by more than the percentage shown in the Table -2 and none deviates by more than twice that percentage.

Table 2: IP standards of percentage of weight variation.

Average weight of capsules	% Deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

Since, the capsules made have the average weight in the range of 480 mg. the limit of % deviation to be taken as ±5.

***In-vitro* dissolution studies**[24]

The dissolution rate of drug from the capsules were studied in two different buffers of pH 1.2 and pH 6.8 with 0.25% of Sodium Lauryl Sulphate using USP (XXIII) dissolution test apparatus employing basket stirrer. The dissolution apparatus had set at speed of 50 r.p.m and a temperature

37 ± 1°C. A 10 ml of aliquot of dissolution medium was withdrawn at different time intervals by pipette by tieing one masculine cloth to the mouth of the pipette. After that it was filtered and assayed by titration method. Similar test was carried out for both formulations.

$$\%Assay = \frac{B.R \times Normality\ of\ NaOH \times avg.wt \times label\ claim \times conversing\ factor}{0.1 \times 0.500}.$$

Assay[25]

Crushed filled powders of 10 capsules of equivalent weight of 300 mg drug were taken. Add some water to make it to dissolve. Add three drops of phenopthalein and three drops of thymol blue as indicator and titrates with 0.IN NaOH. Read the initial and final reading.

RESULTS AND DISCUSSION:

Granules evaluation

The micrometric properties of granules were evaluated by using properties such as angle of repose, bulk density, and compressibility index. The drug content estimation was also determined.

(a) Angle of repose[26]

Angle of repose is determined by fixed funnel method, the results are shown in Table 3.

Table 3: Calculation of Angle of repose of (Fl &F2) granules.

Sample	Height (h) cm	Radius (r) cm	tan θ = h/r	$\theta = \tan^{-1} h/r$	θ_{Avg}
(F1) Granules	1.4	2.3	0.608	34.77	35.55 °
	1.5	2.3	0.652	36.78	
	1.6	2.6	0.615	35.10	
(F2) Granules	1.7	2.4	0.708	39.22	35.26°
	1.3	2.5	0.520	30.52	
	1.4	2.2	0.636	36.06	

The flow properties of the granules were found to be satisfactory because the angle of repose was found to be in the range of 30- 40˚C.

Bulk Density

Bulk density is determined by bulk density apparatus. The results are shown in Tables 4-5.

Table 4: Calculation of True Density for (Fl&F2) granules.

Sample	weight of the granules (g)	True volume (c.c)	True density = wt/volume (gm/c.c)	Average
(F1) Granules	38.4 gm	100	0.384	0.385gm/c.c
	38.6 gm	100	0.386	
(F2) Granules	39.4 gm	100	0.394	0.385 gm/c.c
	37.6 gm	100	0.376	

Table 5: Calculation of Bulk Density for (Fl&F2)) granules.

Sample	weight of the granules (g)	Bulk volume (c.c)	Bulk Density= wt/volume (gm/c.c)	Average
(F1)	38.4 gm	90	0.426	0.425 gm/c.c
Granules	38.6 gm	91	0.424	
(F2)	39.4 gm	91	0.432	0.424 gm/c.c
Granules	37.6 gm	90	0.417	

The lower value of bulk density observed for granules are favorable for filling in capsules.

Compressibility Index[27].

The Compressibility Index are calculated by using the following equation, Compressibility Index I= [1 - v/v°] × 100 and shown in Table 6.

Table 6: Compressibility Index of Formulation (F1&F2) granules

Sample	Untapped vol. of granules, v° (c.c)	Tapped vol. of granules, v (c.c)	I= [1 - v/v°]×100	Average
(F1)	100	90	10	9.5
Granules	100	91	9	
(F2)	100	91	9	9.5
Granules	100	90	10	

As per standard, the value of I below 15% usually give rise to good flow characteristics. So the granules are having good flow properties.

Capsules evaluation (in process parameters):

Results of evaluation of capsules for various parameters are shown as follows on Table-7.

General appearances

Table 7: Results of general appearance evaluation.

Formulations	Colour	Odour	Taste	Shape
(F1)	1. White 2. Lake of sunset yellow 3. Lake of brilliant blue 4. Lake of Quinoline Yellow	Characteristics	No Taste	Zero '0' size
(F2)	1. White 2. Lake of sunset yellow 3. Lake of brilliant blue 4. Lake of Quinoline Yellow	Characteristics	No Taste	Zero '0' size

Physical properties of the capsule

The dimensions determined for formulated capsules were tabulated in the Table 8.

Table 8: Physical properties of the capsules

Batches	Lengths (mm)				
(F1)	20.68	20.68	20.68	20.68	20.68
(F2)	20.52	20.52	20.52	20.52	20.52

Weight variation test

Table 9: Percentage weight variation of (F1&F2) formulation.

Formulation	(Individual weight of the capsules) w_1 mg	Difference(w_1-w) mg	% Deviation	Average Weight in mg
F1	483	-2	-0.343	478.55 mg.
	475	-10	-1.739	All the capsules of (F1) passed
	487	+2	+0.340	weight variation test, as %
	481	-4	-0.688	weight variation was in the
	484	-1	-0.171	pharmacopoeia limits i.e., ±5%.
	483	-2	-0.343	
	486	+1	+0.170	
	487	+2	+0.340	
	482	-3	-0.515	
	486	+1	+0.170	
	484	-1	-0.171	
	480	-5	-0.856	
	479	-6	-1.036	
	484	-1	-0.171	
	487	+2	+0.340	
	489	+4	+0.679	
	481	-4	-0.688	
	486	+1	+0.170	
	484	-1	-0.171	
	483	-2	-0.343	
F2	486	+1	+0.170	479.55 mg.
	484	-1	-0.171	All capsules of (F2) passed
	483	-2	-0.343	weight variation test, as %
	484	-1	-0.171	weight variation was within the
	487	+2	+0.340	pharmacopoeia limits i.e., ±5%.
	484	-1	-0.171	
	480	-5	-0.856	
	479	-6	-1.036	
	484	-1	-0.171	
	487	+2	+0.340	
	489	+4	+0.679	
	481	-4	-0.688	
	486	+ 1	+0.170	
	484	-1	-0.171	
	483	-2	-0.343	
	489	+4	+0.679	
	481	-4	-0.688	
	484	-1	-0. 171	
	487	+2	+0.340	
	489	+4	+0.679	

Dissolution studies:

The data regarding percent drug dissolved obtained from the dissolution tests and the corresponding dissolution profiles are shown in the Table 10

Table 10: Dissolution data for (F1&F2) formulation.

Formulation	Time (hr)	%drug released (B×F)*
(F1)	2	43.00
	4	54.96
	6	63.61
	8	75.73
	10	86.94
	12	99.66
(F2)	2	45.65
	4	57.07
	6	67.71
	8	83.70
	10	88.87
	12	99.66

*each value is an average of three determinations.

CONCLUSION

The work undertaken an attempt was made to timed release veggies capsule of Ginger Root Extract (5%w/w) by using different granules coated with different %age of polymer(ethyl cellulose and hydroxy propyl methyl cellulose k4 m).The purpose was to enhance patient compliance and to provide a sustained effect of drug for a longer action. Three different granules were made by using different % of ethyl cellulose and HPMC as coating agent to get different time release pattern. Two variations had made to fulfill the purpose. In (Fl) formulation 15%, 20% and 25% of ethyl cellulose and 10% of HPMC were used. In (F2) formulation17%. 22% and 25% of ethyl cellulose and 12% of HPMC were used as the coating solution. Dry mix and binding solution were then converted into granules and they exhibited satisfactory values of angle of repose and bulk density. Granules were obtained by wet granulation method then granules are coated by ethyl cellulose and HPMC with various percentage. The capsules were obtained by using clear transparent hard veggie shells of '0' size. Then the capsules were evaluated for the parameters like general appearance, weight variation, disintegration and *in-vitro* dissolution study. Timed release pattern got in the both (F1) and (F2) formulations as required in the 12 hr almost 99% of drug were released. Thus, we are able to achieve our objective of preparing time release capsules of ginger by preparing granules having different percentage of coating solution.

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