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Formulation and Evaluation of Anti-Vertigo Oral Dispersible Tablet

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ABSTRACT
The aim of the present investigation is to formulate &evaluate dispersible tablets by usingdifferent excipients by direct compression method.Thus, the objectives of the present study are to prepare dispersible tablets having least disintegration time so it gives quick drug releasewhich leads to faster onset of action?To evaluate the formulations with respect to various physicochemical parameters.The demand of solid oral drug delivery systems has been growing during the last decadeespecially for geriatric and pediatric patients because of difficulties in administration throughother routes.Hence the present research work is directed towards development of dispersible tablets of Antivertigo drug using direct compression attributed to rapid disintegration of dispersible tablet inwater forming a stabilized dispersion.

Keywords :- Betahistidine HCL, Dispersible, Anti-Vertigo Drug

I. INTRODUCTION

Vertigo is the feeling that you or your environment is moving or spinning. It differs fromdizziness in that vertigo describes an illusion of movement. When you feel as if you yourself are moving, called subjective vertigo, and the perception that your surroundings are moving iscalled objective vertigo. Vertigo is caused by problems in the brain or inner ear, includingsudden head movements, inflammation within the inner ear due to a viral or bacterial inner ear infection, Meniere disease, tumors, decreased blood flow to the base of the brain, multiplesclerosis, head trauma and neck injury, migraine headaches, or complications from diabetes.Symptoms of vertigo include a sensation of disorientation or motion, which may be accompaniedby nausea or vomiting, sweating, or abnormal eye movements. Other symptoms of vertigo mayinclude hearing loss and a ringing sensation in the ears, visual disturbances, weakness, difficultyspeaking, a decreased level of consciousness, and difficulty walking.The most common diseases that result in vertigo are benign paroxysmal positionalvertigo (BPPV), Meniere's disease, and labyrinthitis. Less common causes include stroke, braintumors, brain injury, multiple sclerosis, migraines, trauma, and uneven pressures between themiddle ears. Physiologic vertigo may occur following being exposed to motion for a prolongedperiod such as when on a ship or simply following spinning with the eyes closed. Other causesmay include toxin exposures such as to carbon monoxide, alcohol, or aspirin. Vertigo isclassified into either peripheral or central depending on the location of the dysfunction of the vestibular pathway, although it can also be caused by psychological factors.

Any cause of inflammation such as common cold, influenza, and bacterial infections may causetransient vertigo if it involves the inner ear, as may chemical insults (e.g., amino glycosides) orphysical trauma (e.g., skull fractures). Motion sickness is sometimes classified as a cause ofperipheral vertigo. Benign paroxysmal positional vertigo (BPPV) is the most common vestibulardisorder and occurs when loose calcium carbonate debris has broken off of the otoconialmembrane and enters a semicircular canal thereby creating the sensation of motion. Patients withBPPV may experience brief periods of vertigo, usually under a minute, which occur with changein position.Meniere's disease is a vestibular disorder caused by an increase in the amount of endolymphaticfluid present in the inner ear (endolymphatic hydrops), spontaneous attacks of severe vertigo incombination with ringing in the ears (tinnitus), a feeling of pressure or fullness in the ear (auralfullness), severe nausea or vomiting, imbalance, and hearing loss. As the disease worsens,hearing loss will progress.Labyrinthitis presents with severe vertigo [10] with associated nausea, vomiting, and generalizedimbalance and is believed to be caused by a viral infection of the inner ear. Vertigo that arises from injury to the balance centers of the central nervous system (CNS), oftenfrom a lesion in the brain stem or cerebellum.vertigo and is generallyassociated with less prominent movement illusion and nausea than vertigo of peripheral origin.

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Central vertigo may have accompanying neurologic deficits (such as slurred speech and doublevision), and pathologic nystagmus (which is pure vertical/torsional). Central pathology cancause disequilibrium which is the sensation of being off balance. The balance disorder associatedwith central lesions causing vertigo is often so severe that many patients are unable to stand orwalk.Vertigo is diagnosed by a medical history and physical exam. CT scans, blood tests, magneticresonance imaging (MRI), and electrocardiogram (ECG) may also be performed depending onthe suspected cause.Anti vertigo drugs are vestibular suppressants that attempt to control the sensation of vertigo aswell as associated nausea and vomiting. Vestibular suppressants are often used in conjunctionwith antiemetic. Vestibular suppressants act on the neurotransmitters responsible for carrying thevestibular signal from primary vestibular neurons. That is, these drugs seek to block theconduction of impulses from the semicircular canals and otolith organs, before these nerveimpulses reach central vestibular structures, and thereby maintain tone in the vestibular nuclei.Meniere's disease patients have a variety of treatment options to consider when receivingtreatment for vertigo and tinnitus including: a low-salt diet and intratympanic injections of theantibiotic gentamicin or surgical measures such as a shunt of the labyrinth inrefractory cases. Common drug treatment options for vertigo may include the following:

- Anticholinergicssuch as hyoscine hydro bromide (scopolamine)
- Anticonvulsantssuch as topiramate or valproic acid for vestibular migraines
- Antihistaminessuch as betahistine, dimenhydrinate, or meclizine, which may have antiemetic properties
- Beta blockerssuch as metoprolol for vestibular migraine
- Corticosteroidssuch as methylprednisolone for inflammatory conditions such as vestibularneuritis or dexamethasone as a second-line agent for Meniere's disease.

All cases of decompression sickness should be treated initially with 100% oxygenuntil hyperbaric oxygen therapy (100% oxygen delivered in a high-pressure chamber) can beprovided. Several treatments may be necessary, and treatment will generally be repeated untileither all symptoms resolve, or no further improvement is apparent.In order to prevent the dysphasia and improve patient compliance, orodispersible tablets areintroduced as a substitute in oral DDS, designed to disintegrate in mouth without the aid ofwater. Orodispersible tablets with the aim of giving fast disintegration to the dosage form as itgets in contact with saliva with good agreeable moth feeling. These orodispersible tablets (ODT)can be administered to any patients having difficulty in swallowing. They are also recognized asmouth dissolvable, melt-in-mouth, fast dissolving, rapi-melts or porous tablets.These are tablets which get dispersed or disintegrate when gets in a contact with saliva with therelease of active drug, providing maximum drug bioavailability as compared to conventionaldosage form. This dispersible property is given by the addition of superdisintegrants to thedosage form that releases the drug in mouth increasing the bioavailability.ODTs are developed by the addition of super disintegrants like cross linked cellulose derivative;carboxymethyl cellulose, sodium starch glycolate, Polyvinylpyrrolidone, which gives burstdisintegration when gets in contact with water or salivary secretions. Bioavailability of drugsmay rise due to oral and pregastric absorption, reducing first pass metabolism in gastrointestinaltract.

II. MATERIAL AND METHOD

Betahistine hydrochloride (Gift sample from Intas pharma) , Microcrystalline Cellulose pH 112, Polyvinylpyrrolidone, PVPK 30, Talc, Magnesium Stearate, Mannitol/Lactose Monohydrate, Starch, Sodium Starch Glycolate, Croscarmellose.

Instruments

UV-Visible Double Beam Spectrophotometer (Shimadzu U.V. 1800), FTIR Spectrophotometer (Shimadzu IR Affinity-1), Rotary Tableting machine (CIP Machineries), Tablet hardness Tester (Progressive instruments HT-01), Dissolution Test Apparatus USP (Type-II)- Digital Model (VEEGO Scientific VAD 60), Analytical Balance (Shimadzu AUX 220), pH Meter (EQUIP-TRONICS EQ-610), Vernier Caliper - Digital Model (Mitutoyo MDC-25SB), Disintegration test Apparatus (LABINDIA), Friability Tester (LABINDIA), HPLC (HITACHI ELITE LaChrom).

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Method

Formulation of dispersible tablets of Anti vertigo Drug

The tablets of anti vertigo drug were prepared by using direct compression technique. Accurateamount of the API is mixed with glidant and sifted through sieve #24 and all additives siftedthrough sieve #24. Microcrystalline cellulose granules were prepared by using lab solvent, wetmass is sifted through #8 and keep it in oven at about 10 min. for drying and dry granules siftedthrough sieve #16 were homogeneously blended in geometric dilutions. Magnesium stearate andstarch were taken previously sifted through #24 and added as a lubricant to the blend in apolybag. These blended mixtures were compressed by using tablet compression machine having8 mm, flat face punch having inscription 'BKP Institute of Pharmacy' on one side and a breakline on the otherside. A weight of 180mg was maintained for all the tablets. Compositions of each formulation are given in Table No.1.

Table No. 1: Formulation of Dispersible Tablets of Anti Vertigo

Ingredients	**F1**	**F2**	**F3**
Betahistine HCl	8	8	8
MCC 112	75	75	75
Polyvinylpyrrolidone	4	4	4
PVPK 30	4	4	4
Talc	10	10	10
Mg. Stearate	4	4	4
Mannitol/ Lactose Monohydrate	35	30	25
Starch	10	10	10
Sodium Starch Glycolate	5	10	15
Croscarmellose	5	5	5
Starch (For Lubrication)	20	20	20
Total Weight (mg)	180	180	180

Evaluation of Tablets

Preformulation Studies

Characterization of API

Determination of UV Spectrum:

A 1000 µg/ml stock solution of API was prepared by dissolving 50 mg of the drug in 50 ml of pH 6.8 Phosphate buffer solutions. The λ max of API was determined by scanning suitable dilutions under UV Spectrophotometer.

Determination of Infra Red Absorption Spectrum:

IR absorption spectrum of API was recorded by FTIR technique, where 1-2 mg of drug sample was used. The resultant spectrum of the drug was compared with a reference spectrum of API.

In the Present work , Preformulation study was performed with different parameters like Angle of repose, Bulk density &Tapped density, Carr's compressibility index, Hausner's ratio.Results are shown in Table no 5.

Post- compression parameters

Physical Characterization of tablets:

Twenty tablets were randomly selected from the prepared formulations and examined forshape, thickness ,diameter.

Hardness:

Five tablets were randomly selected from each formulation and hardness of the same wasdetermined by using hardness tester. Average value was calculated and was expressed inKilogram per centimeter square (kg/cm2).

Weight variation:

To study weight variation, 20 tablets were selected randomly from a batch and were individuallyweighed and then the average weight was calculated. The tablets meet the IP specifications if notmore, than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 timesthe percentage limits.

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Table 2: Limits for Weight variation'

Dosage form	Average weight of tablet (mg	% deviation
Uncoated and film coated tablets	80 mg or less	10
	More than 80 mg but not less than 250 mg	7.5
	250 mg or more	5

Friability:

Friability test is performed according to USP specifications using LABINDIA friabilator. Arandom sample of 20 tablets was dedusted, accurately weighed, and placed in the drum of aLABINDIA Friability tester. Drum was rotated 100 times and tablets were removed, dedusted,and accurately weighed. The percentage friability was calculated by,F = W initial – W final / W final x 100% Friability of tablets less than 1 % is considered acceptable.

In-vitro Disintegration Study:

The in-vitro disintegration test for prepared tablets was carried out using LABINDIADisintegration Test Apparatus. Six tablets were placed individually in each tube of disintegrationtest apparatus and Discs were placed over each tablet. Distilled water was used as the mediumwhich is maintained at 37 ± 2°C and the time taken for each tablet to disintegrate completely wasrecorded.

Uniformity of drug content:

Determine by liquid chromatography.

Test solution: Crush one tablet in 100 ml volumetric flask. Add about 50 ml of mobile phase andswirl for 10 minutes, make up to volume with mobile phase and filter.

Reference solution: A 0.032 per cent w/v solution of API RS in mobile phase.

Chromatographic systemA stainless steel column 25 cm x 4.6 mm packed with octadecylsilyl silica (5µm),Column temperature 50°, Mobile phase: dissolve 2.76 g of sodium dihydrogen phosphate monohydrate and 1.6 g ofsodium dodecylsulphate in 600 ml of water, add 0.4 g of hexylamine and 400 ml ofacetonitrile, adjust the pH to 3.5 with orthophosphoric acid,Flow rate 2 ml per minute,Spectrophotometer set at 254 nm,A 20 µl loop injector.Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0,the column efficiency in not less than 2000 theoretical plates. The relative standard deviation forreplicate injections is not more than 2.0 per cent.Inject the test solution and reference solution.Calculate the content of API.

In-vitro Drug Dissolution study:

In-vitro dissolution study was carried out using USP dissolution test apparatus type II. Thedissolution medium used was 900ml of buffer solution prepared by dissolving 21.9 g ofanhaydrous disodium hydrogen orthophosphate and 4.83 g of citric acid in 1000 ml of water,adjust pH to 6.8 with 1M NaOH, which was maintained at 37°C±1°C. The paddle speed waskept at 50 rpm throughout the study. A 5ml of sample was withdrawn at 30 min interval anddiluted adequately. Measure absorbance of filtered solution, suitably diluted with medium ifnecessary, at maximum at about 256 nm. Calculate content of drug in medium from absorbanceobtained from a solution of known concentration of drug in same medium.

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III. RESULT & DISCUSSIONS

Characterization of API

Determination of UV Spectrum:

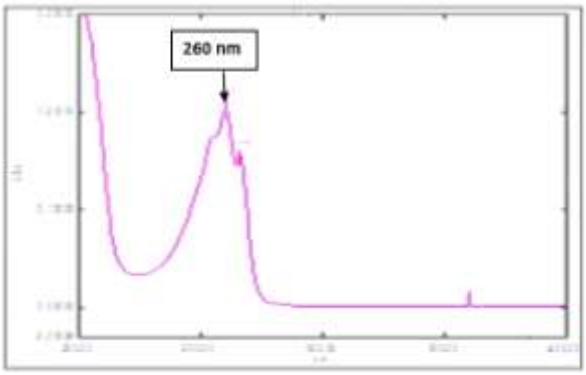
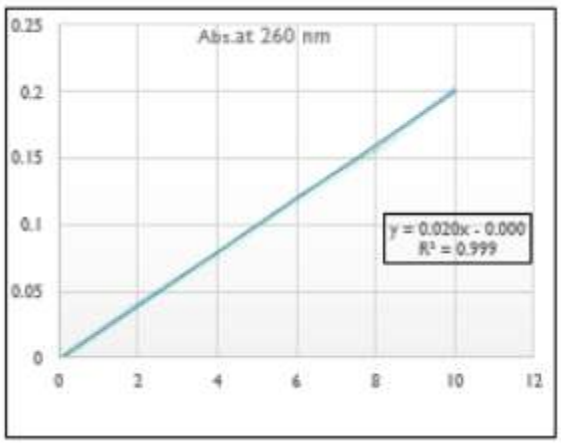


Fig. No.1: λ_{max} of API in phosphate buffer (pH 6.8) solution

Calibration curve of Betahistine HCl in Phosphate Buffer pH 6.8

Concentration (µg/ml)	Absorbance at 260 nm
2	0.04134
4	0.07918
6	0.12073
8	0.15706
10	0.20367



Graph 1 :- Calibration Curve of Betahistine HCL

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Determination of Infra Red Absorption Spectrum of API

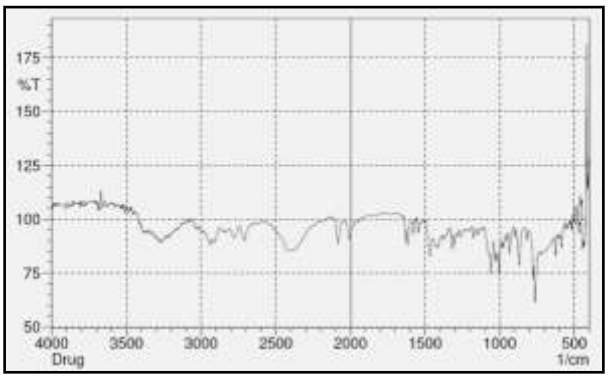

Fig. No.2: Infra Red Spectrum of API

Interpretation of IR Spectra of Drug

The IR spectrum of API reveals the presence of major functional group in the structure of API supporting its identity.

Table No.4: Peaks observed in Infrared Spectrum of API

Wave Number (cm^{-1})	**Corresponding Functional Group and Type of Molecular Vibration**
3212	N-H Stretching
1349	C=N Stretching
1600	C=C Stretching

Evaluation of Tablets:

Pre compression parameters:

Precompression studies of all formulation showed acceptable flow properties with respect to angle of repose and Housner's Ratio. The values of Carr's Index showed that satisfactory packing ability of the formulations. The results of precompression parameters analysis were given in table no.5.

Table No.5: Pre-compression parameters of all the formulations

Formulation code	**Bulk Density (gm/cm^2)**	**Tapped Density (gm/cm^2)**	**Carr's Index (%)**	**Housner's ratio**	**Angle of Repose (Ɵ)**
F1	0.40	0.54	17.18	1.20	26.91
F2	0.50	0.56	15.54	1.18	28.23
F3	0.50	0.58	13.79	1.19	29.34

Post-compression parameters

- **Physical Characterization of Tablets:**

Physical characterization of all formulations showed that prepared tablets were flat, circular shape and off-white in color having thickness ranged from 2.616±0.042 mm to 2.802±0.047 mm. The standard deviation values indicated that all the formulations were within the

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Indian Pharmacopeial range (± 0.2 mm). The results of thickness for tablets were shown in Table No.6.

- **Hardness:**

The hardness of all the tablets prepared by direct compression methods was found to be within 4kg/cm2 to 5kg/cm2 which is acceptable. The mean hardness test results are tabulated in Table No.6.

- **Friability test:**

The friability of all the tablets prepared by direct compression methods was found to be nil (zero). The values were found to be within the limit (<1%) in all designed formulations. Thus tablets possess good mechanical strength & comply with the pharmacopoeial standard. The results of friability for tablets were shown in Table No.6.

- **Weight variation test:**

The weight variation of all the tablets was found between 160±0.0030 mg to 190±0.0044 mg which is within Pharmacopeial limit. Thus was acceptable. The results of weight variation for tablets were shown in Table No.6.

- **The in-vitro disintegration time:**

The in-vitro disintegration time is measured by the time taken to undergo complete disintegration. Rapid disintegration within several minutes was observed in all the formulations. The in-vitro disintegration data is tabulated in table no.9.6. All the formulations showed disintegration time less than 3 minutes due to wicking and swelling mechanism of superdisintegrants. The in-vitro disintegration time of tablets were found to be in the range of 1min 05 sec. to 2min 53sec fulfilling the official requirements.

Table No.4: Post-Compression Parameters of All Formulations

Formulation code	Hardness (Kg/ cm2)	Thickness (mm) (n=5)	Friability (%)	Weight variation (n=20) Mg	In vitro Disintegration time (min)
MKTD	6	2.442±0.010	0	117±0.0041	2.15
F1	6	2.616±0.042	0	165±0.0047	2.05
F2	5	2.718±0.029	0	165±0.0048	1.43
F3	4	2.76±0.017	0	164±0.0044	1.53

- **Drug content:**

As per Indian Pharmacopoeial specifications, the drug content should be in range of not less than 95% and not more than 105%. Based on results of test for content uniformity, **Formulation no.F1** shows 99.86% of drug content & hence passed the test. The results of drug content for tablets were shown in Figure No.3.

Fig. no.3: Drug content uniformity test Sample 1 In-vitro dissolution studies:

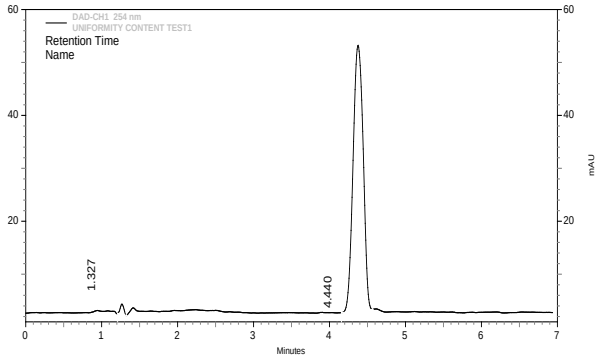

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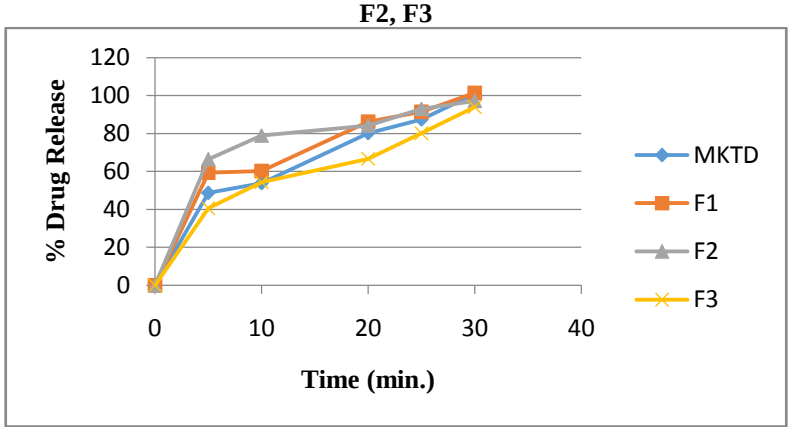
Table No.7: In vitro dissolution studies

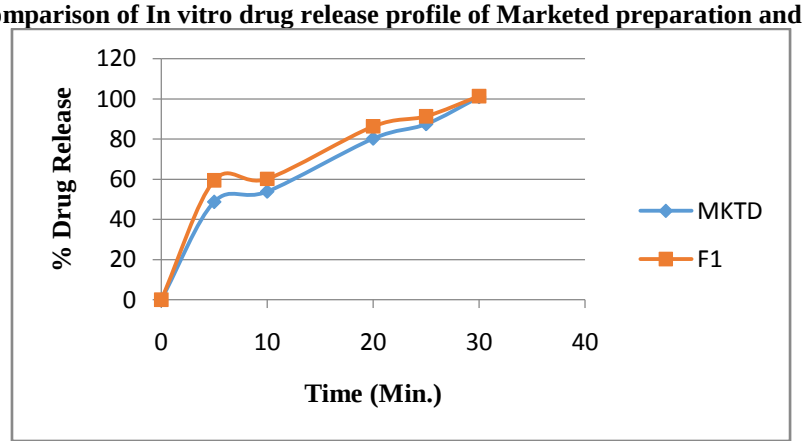
Time (min)	MKTD	F1	F2	F3
0	0	0	0	0
5	48.67941	59.38676	66.44515	40.64956
10	53.80721	60.16669	78.93385	54.39789
20	80.16493	86.255	84.22767	66.72973
25	87.37037	91.3364	93.01603	80.18723
30	100.8207	101.3537	97.17877	94.02186

Results of in vitro dissolution studies showed that Formulation No. F1 containing Lactose monohydrate used as a diluent the percent drug release values decreased with increase in concentration of sodium starch glycolate. The percent drug released of F1, F2 and F3 was found to be 101.35%, 97.17 and 94.02% respectively. Hence, the release profile indicated that Lactose monohydrate which is used as diluents is better than dicalcium phosphate & mannitol as diluents to formulate dispersible tablets.

Graph No.2: Comparison of In vitro drug release profile of Marketed preparation and formulation F1, F2, F3



Graph No.3: Comparison of In vitro drug release profile of Marketed preparation and formulation F1



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