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Formulation and evaluation of bilayered tablet of Piracetam and Vinpocetine

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ABSTRACT

The aim of present work was the formulation of Bi-layer tablets of Piracetam and Vinpocetine, so that synergistic effect of this combination could be used for the effective treatment of Alzheimer Disease. Wet granulation process was used for the formulation of both layers and the final film coated tablets were evaluated for the thickness, weight variation, hardness, friability, disintegration time, dissolution study. Among the formulation, tablets of batch V2 of vinpocetine & batch P3 of piracetam was taken as optimized formula due to its higher rate of dissolution and complied all the other parameters with the official specifications. The stability study of the selected formulations was done at 40˚C and 75% RH for 3 months. It was concluded that Piracetam, Vinpocetine Bi-layer tablets can be prepared successfully as it satisfies all the criteria as a Bilayered tablet and would be alternative to the currently available conventional tablets.

Keywords: Piracetam and Vinpocetine, Bi-layered tablets, Wet granulation process.

INTRODUCTION

Now-a-days for the effective treatment of various diseases and disorders requiring long term therapy such as cancer, tuberculosis, hypertension and diabetes, combination therapy is preferred. As combination therapy has various advantages over monotherapy such as problem of dose dependent side effects are minimized. A low-dose combination of two different agents reduces the dose-related risk; the addition of one agent may counteract some deleterious effects

of the other. Using low dosage of two different agents minimizes the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet and thus dosage of the single component can be reduced [2].

The term Bi-layered tablet refers to tablet containing two subunits that may contain same or two to three different drugs. Bilayered tablet allows for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release while second layer designed to release drug latter, either as second dose or in an extended release manner [1, 2, 6, 8, 12]. Bilayered tablets are also prepared with an approach of gastro retention like Floating bioadhesive bilayer tablet [7, 9, 13]. Drug having short plasma half-life could suitably be formulated as bilayered tablets having one immediate release layer, for fast release of drug using Superdisintegrants causing sudden rise in plasma drug concentration followed by slow release of same drug from sustained release layer using different polymers, which will ultimately maintain its plasma drug concentration [8]. Bi-layer tablet are also formulated to separate physically or chemically incompatible ingredients [6]. Atmost care has to be taken during bilayer tablet formulation to overcome common bi-layer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc [10].

This study shows how to formulate the Bi-layered tablets of piracetam and vinpocetine that can be used for the treatment of various cerebro-vascular diseases or for treating various psychic or neurological symptoms .Piracetam (2-oxo-1-pyrrolidine acetamide) is a cyclic derivative of neurotransmitter GABA & the first representative of what are commonly known as the ‘Smart’ or ‘nootropic’ drugs (Nootropic means "acting on the mind") originally marketed in 1971 by UCB Pharma. It is an agent that acts on cognitive function without causing sedation or stimulation. It is a water-soluble pyrrolidone derivative, chemically similar to Pyroglutamate. It has been found to increase blood flow and oxygen consumption in parts of the brain and to protect against the effects of hypoxia. Piracetam may facilitate movement of information between the brain's two hemispheres via the corpus callosum, and improves the function of the neurotransmitter acetylcholine via muscarinic cholinergic (ACh) receptors which are implicated in memory processes. It may also have an effect on NMDA glutamate receptors which are involved with learning and memory processes. Piracetam is also thought to increase cell membrane permeability and may exert its global effect on brain neurotransmission via modulation of ion channels (i.e., Ca^{2+}, K^{+}) [3, 4, 5, 14, 16, 18]. Second drug, vinpocetine is a poorly-water soluble semi-synthetic derivative of vincamine. Vincamine is an alkaloid derived from the plant *Vinca minor L.*, a member of the periwinkle family. Vinpocetine, as well as vincamine, are used in Europe, Japan and Mexico as pharmaceutical agents for the treatment of cerebrovascular and cognitive disorders. It is sometimes called a nootropic, meaning cognition enhancer. Vinpocetine oxygenate and activate cerebral metabolism and it has several possible actions, including increasing cerebral blood flow and metabolism, anticonvulsant, cognition enhancement, neuroprotection, increased tolerance of the brain to vascular hypoxia and ischemia, lowering of blood viscosity and antioxidant. Vincamine, the parent compound of vinpocetine, is believed to be a cerebral vasodilator.Vinpocetine has been reported to have calcium-channel blocking activity, as well as voltage-gated sodium channel blocking activity. It has also been reported to inhibit the acetylcholine release evoked by excitatory amino acids and to protect neurons against excitotoxicity. In addition, vinpocetine has been shown to inhibit a cyclic GMP

phosphodiesterase, and it is speculated that this inhibition enhances cyclic GMP levels in the vascular smooth muscle, leading to reduced resistance of cerebral vessels and increase of cerebral flow. Experiments with vinpocetine indicate that it can dilate blood vessels, improve oxygen utilization, make red blood cells more pliable, and inhibit aggregation of platelets. Vinpocetine is a preventive anti-stroke remedy. Arteriosclerosis progression in brain is retarded. Both Vinpocetine (with cerebro protecting properties) and Piracetam (with nootropic properties) easily pass the blood brain barrier [4, 14, 16, 18].

Multi layer tablets are made by compressing different granulations fed into the die in succession, one on top of another, in layers, and have the appearance of a sandwich, because, the edges of each layer are exposed. Each layer comes from a separate feed frame with individual weight control. Monograms and other distinctive markings may be impressed on the surfaces of the multi-layered tablets. Analytical work may be simplified by separation of the layers prior [6]. Incompatible substances can be separated by formulating them in separate layers as a two layer tablets or separating the two layers by a third layer of an inert substance as a barrier between the two [1]. Layers may be colored differently to identify the product. Bi-layer tablets are very common for drugs such as glimepiride, metformin hydrochloride, captopril, metoprolol, amoxicillin and potassium clavulanate, propranalol hydrochloride, bambuterol hydrochloride etc.

EXPERIMENTAL SECTION

Material: All the materials used were of analytical grade and procured from commercial sources.

Preparation of Bi-layer tablets:

Piracetam and vinpocetine Bi-layer tablets were prepared by wet granulation process according to the formula given in the table-1. Up to three formulations are prepared for bilayer tablet. First Piracetam layer is prepared by sifting the materials shown in table-1, through the sieve separately. Then binding agent is prepared by dissolving PVP k-30 in specified quantity of purified water, also methyl paraben & propyl paraben are dissolved in it. Load the sifted piracetam, maize starch in a rapid mixer granulator. Add the binding agent which is previously prepared. Dry the damp mass in dryer. Then pass the dried granules through sieve no# 60.Then mix the above granules with lubrication (mixture of Talc, SSG, maize starch, magnesium stearate, colloidal anhydrous silica) for 10-15 mins. Similarly Vinpocetine layer is prepared by sifting all the material shown in table-1, then mix vinpocetine & M.C.C. geometrically. Add lactose & maize starch to it. Then binding agent is prepared by dissolving maize starch in specified quantity of purified water, also dissolve color into it. Then the tablets were compressed by using the double-sided tablet press that has been specifically designed and developed for the production of quality Bi-layer tablets. Piracetam layer blend is initially pre-compressed with low hardness and Vinpocetine layer blend is compressed over it, till the desired hardness is achieved. This technology is called Bi-layered technology. Bi-layered tablets are coated by coating machine using film coat material. Before tablet preparation the mixture blend of all formulations are subjected to preformulation studies like bulk density, tapped density, compressibility index (%), Hausner's ratio and angle of repose [6, 11,15].

Evaluation of tablets:
The prepared tablets can be evaluated for various official and non official specifications [3, 11, 15, 17].

Thickness:
The thickness of the tablet is measured by vernier calipers scale. Thickness of the tablet related to the tablet hardness and can be used an initial control parameter.

Weight variation:
Twenty tablets were selected at random and average weight was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness, Friability:
Tablets were evaluated for hardness and friability test using schleuniger hardness tester and Roche friabilator respectively.

In-vitro Disintegration time:
A tablet was placed in each of the six tubes of the basket. Suspend the assembly in water maintained at a temperature of 37 ± 2^0C and operate the apparatus, simultaneously note the time tablet takes to disintegrate completely.

Drug content:
The drug content was determined by HPLC.

HPLC CONDITION:
Apparatus: High Pressure Liquid Chromatography
Column: C_{18} 250×4.6 mm, 5µm (Hypersil BDS)
Flow Rate: 1 ml/min
Wavelength: 225 nm
Injection volume: 10 µl
Diluent: mobile phase
Detector: PDA (Photodiode Array)
Mobile phase: 0.005 M ammonium acetate (adjust pH 4.5 using acetic acid): ACN = 40:60

Standard solution: weigh 40 mg piracetam transfer in of 50 ml volumetric flask. Add 5 ml of 100 ppm vinpocetine solution (made in mobile phase, 10 mg vinpocetine diluted to 100 ml mobile phase).Add few ml of mobile phase to it. Sonicate for 20 min. Make up the volume upto 50 ml. filter the solution using 0.45µm membrane.

Sample solution: Triturate 20 tablets. Weigh 600 mg of powder and transfer into 50 ml volumetric flask. Add mobile phase to it. Sonicate for 20 min. Makeup the volume upto 50 ml. Filter 1ml of above solution to 10 ml with mobile phase. Filter the solution using 0.45µm membrane.

In-vitro drug release study:

PIRACETAM: An in-vitro drug release study was carried out using tablet dissolution test apparatus USP type-2(paddle) at 50rpm.The dissolution medium consisted of 900ml acetate buffer pH 4.0, maintained at a temperature 37±0.5^{0}C. A sample of 10ml was withdrawn at predetermined time intervals (sample is filtered using 0.45 µm) and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. The 10ml withdrawn sample was diluted to 50ml and then measure absorbance by HPLC technique.

HPLC CONDITION:
Apparatus: High Pressure Liquid Chromatography
Column: C_{18} 250×4.6 mm, 5µm (Hypersil BDS)
Flow Rate: 1 ml/min
Wavelength: 225 nm
Injection volume: 10 µl
Diluent: Acetate buffer pH 4.0
Detector: PDA (Photodiode Array)
Mobile phase: Mixture of Buffer: Acetonitrile = 900:100, filter and degas.

Buffer: Weigh accurately about 1.0 gm of Dipotassium Hydrogen Ortho Phosphate into 1 liter volumetric flask and make up with water.

Standard solution: Weigh accurately about 40 mg piracetam working standard into 100 ml volumetric flask. Add 50 ml of dissolution media, Sonicate for 20 minutes and makeup with dissolution media to produce 100 ml, mix thoroughly. Pipette out 10 ml of this solution into 50 ml volumetric flask and makeup with dissolution media. Filter the solution using 0.45µm membrane.

Sample solution: 10 ml of sample was withdrawn at each time interval and it was filter using 0.45µm membrane. This 10ml withdrawn sample was diluted to 50ml with the dissolution media. Filter this solution using 0.45µm membrane.

VINPOCETINE: An in-vitro drug release study was carried out using tablet dissolution test apparatus USP type-2(paddle) at 100rpm.The dissolution medium consisted of 500ml 0.1N HCl, maintained at a temperature 37±0.5^{0}C. A sample of 10ml was withdrawn at predetermined time intervals (sample is filtered using 0.45 µm) and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Then measure the absorbance by UV at 268.5nm

RESULTS AND DISCUSSION

Preformulation study:
The values of preformulation parameters evaluated were within prescribed limit and indicated good fine flow property (table-2).

Post-compression parameters:

The data of evaluated tablets such as thickness, weight variation, hardness, friability, and In-vitro disintegration time, Drug content, are shown in (table-3). The percentage drug release in bi-layer tablets of P3V2 batch for Piracetam when compare with Piracetam innovator was found to be in the range 86.18 to 101.58 % & the percentage drug release for Vinpocetine in bi-layer tablets of the same P3V2 batch when compare with Vinpocetine innovator was found to be in the range 96.8 to 101.2 %.Whereas the percentage drug release in bi-layer tablets of P4V2 batch for Piracetam when compare with Piracetam innovator was found to be in the range 38.42 to 96.09 % & the percentage drug release for Vinpocetine in bi-layer tablets of the same P4V2 batch when compare with Vinpocetine innovator was found to be in the range 77.50 to 95.00 % and the results are shown in the table-4 along with figures 1, 2. While the in-vitro disintegration time was found to be 3.53 & 12.23 min. for P3V2 & P4V2 batches respectively.

Table No.1- Comparative data of various formulations: Piracetam & Vinpocetine

FORMULATION DATA FOR PIRACETAM					**FORMULATION DATA FOR VINPOCETINE**		
Ingredients	**Formulation code (Quantity per tablet)**				**Ingredients**	**Formulation code (Quantity per tablet)**	
	P1(mg)	**P2(mg)**	**P3(mg)**	**P4(mg)**		**V1 (mg)**	**V2 (mg)**
Piracetam	400	400	400	400	Vinpocetine	5	5
Maize starch	59.21	55.36	63	51.36	Lactose	34.36	34.36
P.V.P K-30	10	16	16	20	Maize starch (for paste)	5.5	5.5
Sod. Methyl paraben	0.12	0.12	0.12	0.12	Maize starch	17.72	17.72
Sod. Propyl paraben	0.012	0.012	0.012	0.012	M.C.C.	29.42	28.1
Water	Q.S.	Q.S.	Q.S.	Q.S.	Color (quinoline yellow)	0.5	0.5
Talc	6	6	6	6	Water	Q.S.	Q.S.
SSG	12	12	12	12	Mg. stearate	0.5	0.55
Maize starch	6.5	6.5	-	6.5	Talc	1.5	2.77
Mg. stearate	1.5	1.5	1.5	1.5	S.S.G.	5.5	5.5
Aerosil	2.5	2.5	2.5	2.5			
Total composition	**500**	**500**	**500**	**500**	**Total composition**	**100**	**100**

TableNo.2-Micromeritic properties of powder blend

Drugs	**Formulation**	**Bulk density (gm/ml)**	**Tapped density (gm/ml)**	**Angle of repose(θ)**	**Compressibility index (%)**	**Hausner's Ratio**
Piracetam	P1	0.5242	0.6913	32.75	24.17	1.31
	P2	0.5878	0.6894	27.11	14.73	1.17
	P3	0.6002	0.6524	26.68	8.00	1.08
	P4	0.6048	0.6573	26.00	7.98	1.08
Vinpocetine	V1	0.5501	0.6998	30.63	21.39	1.27
	V2	0.5684	0.6459	26.55	11.99	1.13

Table No.3 Evaluation of bilayer Tablets

Formulation Code	**Thickness (mm)**	**Weight Variation (mg)**	**Hardness (kg/cm^2)**	**Friability (%)**	**In-vitro Disintegration Time (sec)**	**Drug content (%)**	
						Piracetam	**Vinpocetine**
P3V2	4.64	603	14.5	0.19	3.54	101.9	101.8
P4V2	4.63	604	20.0	0.11	12.23	101.5	100.7

Table No.4 In-Vitro dissolution profile of various formulations

Time (min)	Piracetam (innovator)	Vinpocetine (innovator)	% Drug Release			
			P3V2		P4V2	
			P3	V2	P4	V2
0	0	0	0	0	0	0
10	30.00	86.7	86.18	96.80	38.42	77.50
15	40.48	88.0	94.12	97.90	55.00	81.80
20	50.01	89.4	99.78	98.60	90.52	83.70
30	62.15	93.5	100.12	101.0	91.34	89.80
45	78.66	97.3	101.58	101.2	96.09	97.00
60	88.06	99.1	100.54	98.5	95.84	95.00

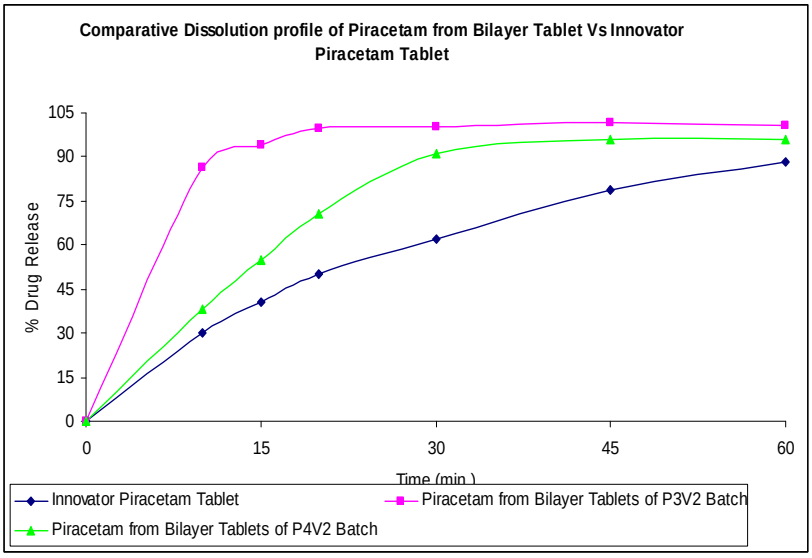

Figure.1-Comparison of dissolution profile of Innovator Drug (Piracetam) and P3, P4 (Piracetam) in pH 4.0 Acetate buffer.

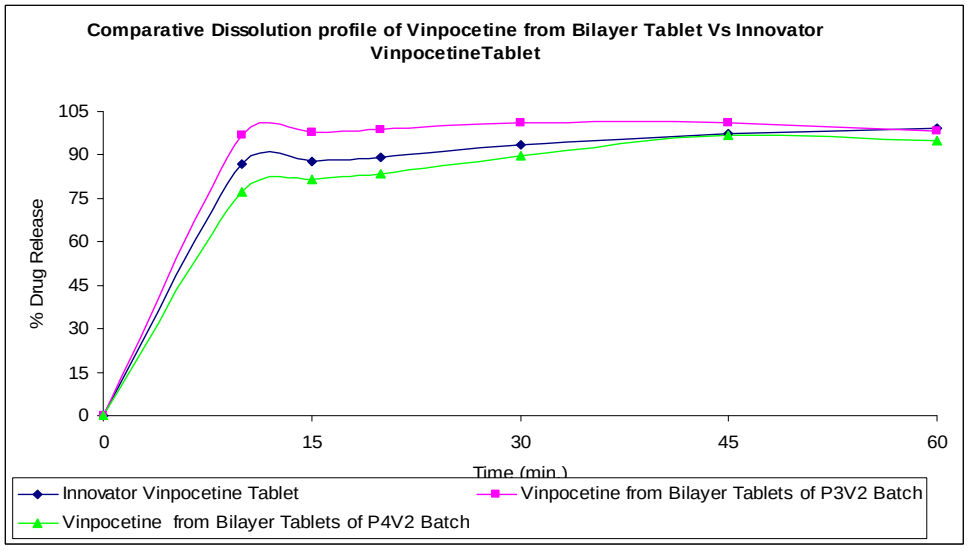

Figure.2-Comparison of dissolution profile of Innovator Drug (Vinpocetine) and V2 in P3V2, V2 in P4V2 in 0.1N HCl buffer.

In the present study Piracetam and Vinpocetine bilayered were prepared by wet granulation process by using ingredients shown in (table-1). A total number of three formulations were prepared for bilayer tablet. The hardness was found to be in the range of 12kp to 20kp, the normal acceptance criteria for hardness are not more than 25.00kp [2]. All the formulation has got hardness in the acceptable range and was considered acceptable upon comparing with the innovator product. But P1 batch was found to have friability greater than 1.0% (The normal acceptable criterion for friability is not more than 1.0% [2, 11].) and V1 batch had poor flow which led to weight variation problem, so this batches were rejected. All the formulations indicate good thickness. The bilayer tablets were prepared by compressing P2 batch of piracetam with V2 batch of vinpocetine, P3 batch of piracetam with V2 batch of vinpocetine & P4 batch of piracetam with V2 batch of vinpocetine. The bilayered tablet batch P2V2 showed layer separation so it was rejected, whereas the other two batches of P3V2 & P4V2 were accepted for further analysis. Formulation P3V2 nearly matches with the disintegration time of innovator product whereas formulation P4V2 is acceptable since as per official limit of the disintegration time of an immediate release tablet that should be less than 15 mins [2]. Among the formulated batches, tablets of batch P3V2 containing Piracetam 400 mg and Vinpocetine 5 mg per tablet is similar and equal to the innovator product in respect of all tablets properties and dissolution rate and showed good hardness, low friability, and disintegration time of 3.53 min. The percentage drug release for formulation P3V2 shows the better drug release between 101.20 to 101.58 %. Thus it was accepted as optimized batch.

CONCLUSION

The formulated tablet showed good release as compared to the innovator tablets. Moreover atmost care needs to be taken while formulation of bilayer tablet to avoid layer separation and weight of both layer needs to be controlled properly. It was concluded that Piracetam, Vinpocetine Bi-layer tablets can be prepared successfully as it satisfies all the criteria as a Bilayered tablet and would be alternative to the currently available conventional tablets.

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