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PREFORMULATION AND PRELIMINARY STUDY ON THE USE OF NATURAL POLYMERS FOR THE DEVELOPMENT OF ORODISPERSIBLE TABLET USING CUT AND WEIGH METHODS

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Abstract:
The complexity in the physicochemical characteristics of drugs and there In Vivo fate needs the quality of polymers to be that which could suppress the enzymatic action over drugs. The emergence of technology in an extraction procedure of herbal products has led to the development of various natural polymers which ensures the development of such dosage form that could easily deceive various factors affecting the degradation of drug within the body. The use of synthetic polymers in the formulation of orodispersible tablet was very common but high dispersion time, low hardness and failure in friability were the main reasons which led to the use of natural polymers like chitosan, gum tragacanth and gum karaya for the development of orodispersible tablet. But before formulation development the determination of preformulation studies as well as preliminary studies are main to carried down so, in this paper Preformulation studies of Venlafaxine hydrochloride for UV identification, solubility studies and lipophilicity was carried out. Similarly, preliminary studies of micromeritics properties and placebo formulations with their evaluation using cut and weigh methods were carried out.

Keywords: ***Orodispersible tablets, Venlafaxine hydrochloride, gum karaya, gum tragacanth, Preformulation studies.***

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INTRODUCTION:

The BCS is a scientific framework for classifying a drug substance on the basis of solubility as well as lipophilicity [1] Table 1. The classification system set up prerequisite conditions of determination for dosage form design considering absorption and distribution of drug within the blood plasma as well in biological membranes [2]. Venlafaxine Hydrochloride is class I drug with a solubility of 572 mg/mL in water and octanol:water (0.2 M sodium chloride) partition coefficient of 2.69. Drug belongs to class of serotonin and norepinephrine reuptake inhibitors (SNRIs) which aids in the increase in the levels of serotonin and noradrenaline in the brain and mainly used as antidepressant drug [3]. Venlafaxine hydrochloride is designated as (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethylamino)methyl]–p-methoxybenzyl] cyclohexanol hydrochloride. Through literature study it was depicted that 92% of a single oral dose of drug could be adsorbed. On contrary, picture of bioavailability data was something epic as only 45% of parent drug reaches to systemic circulation. The detailed study assured the possible reason behind was the metabolism of drug into another active metabolite O-desmethylvenlafaxine (ODV). Such extensive first pass metabolism confirmed the recognition of active group by cytochrome enzyme over Venlafaxine Hydrochloride. The literature review also revealed that the active metabolite produced was more potent as compared to pure drug with enhanced therapeutic action and even in presence of active metabolite in blood the therapeutic efficiency of pure drug generally decreases [4]. So, from above study it was revealed that on administration through oral route only the active metabolite produced would be favorable while rest of pure drug in systemic blood is of no use. In that case, the duty of formulation scientist is to increase the metabolism of drug but in reality that was not reported in any literature. So, the aim of this study was to design a dosage form that could easily bypass the first pass metabolism as in absence of active metabolite pure drug showed more therapeutic action. There are various routes that can bypass metabolism but as drug has antidepressant action so best route must be through oral cavity and development of orodispersible tablet was the chosen dosage form for this study. There were various polymers used in previous studies with dispersible nature but very less papers were present in which natural polymers were used for orodispersible action. The rationale behind using natural polymers was to increase the hardness of tablet as reported synthetic polymers used for orodispersible action were mainly suffers from poor hardness as well as friability [5]. The use of natural polymers having high binding properties and swelling properties was the main task of this study [6]. But before developing any dosage form, preformulation for determining any interaction between active pharmaceutical ingredient (API) and polymers is must. Preformulation studies (physicochemical and biopharmaceutical properties) provide valuable information about druggability during lead identification and optimization [7]. So, in this study various preformulation testing to design an appropriate dosage form and preliminary studies for the development of orodispersible tablet with cut and weigh methods were performed for comparing the efficiency of natural polymers as compared to synthetic polymers.

Table 1: The Biopharmaceutical Classification System

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

MATERIAL AND METHODS:

Venlafaxine hydrochloride obtained as a gift sample from Cadila pharmaceuticals India, Chitosan, Gum tragacanth, Gum karaya, sodium starch glycolate, sodium carboxymethyl cellulose form Central drug house and all other chemicals used were of HPLC grade.

Table 2: Composition of different batches of formulation

Formulation code	Drug (mg)	Chitosan (mg)	Gum Tragacanth (mg)	Gum Karaya (mg)	Sodium starch glycolate (mg)	Sodium Carboxy Methyl Cellulose (mg)	Mannitol (mg)	MCC (mg)	Aspartane (mg)	Magnesium stearate (mg)	Talc (mg)
FC1	-	6					80	70	15	2	2
FC2	-	12					80	64	15	2	2
FC3	-	18					80	58	15	2	2
FG1	-		6				80	70	15	2	2
FG2	-		12				80	64	15	2	2
FG3	-		18				80	58	15	2	2
FK1	-			6			80	70	15	2	2
FK2	-			12			80	64	15	2	2
FK3	-			18			80	58	15	2	2
FS1	-				6		80	70	15	2	2
FS2	-				12		80	64	15	2	2
FS3	-				18		80	58	15	2	2
FM1	-					6	80	70	15	2	2
FM2	-					12	80	64	15	2	2
FM3	-					18	80	58	15	2	2

Preformulation Studies **[8],[9]**

The investigation of physical and chemical properties of drug was determined as the first step in the rational development of dosage form.

UV spectrophotometric analysis of drug: The wavelength of maximum absorption of a drug 40µg/ml in methanol was determined by scanning at 200 to 400nm.

Standard curve of Venlafaxine Hydrochloride in phosphate saline buffer pH 7.4: Weighed amount of 10mg of pure drug was dissolved into 10 ml of buffer to make 1000µg/ml of solution. From this stock solution sub stock solution was prepared by diluting 2.5ml of stock upto 25ml of buffer to obtain 100 µg/ml of solution. The further dilution was made by diluting 1ml, 2ml, 3ml, 4ml and 5ml of sub stock upto 10ml of buffer to obtain 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml and 50µg/ml of diluted solutions. These dilutions were then scanned using UV spectrophotometer to determine absorbance and finally standard curve was plotted between absorbance and concentration.

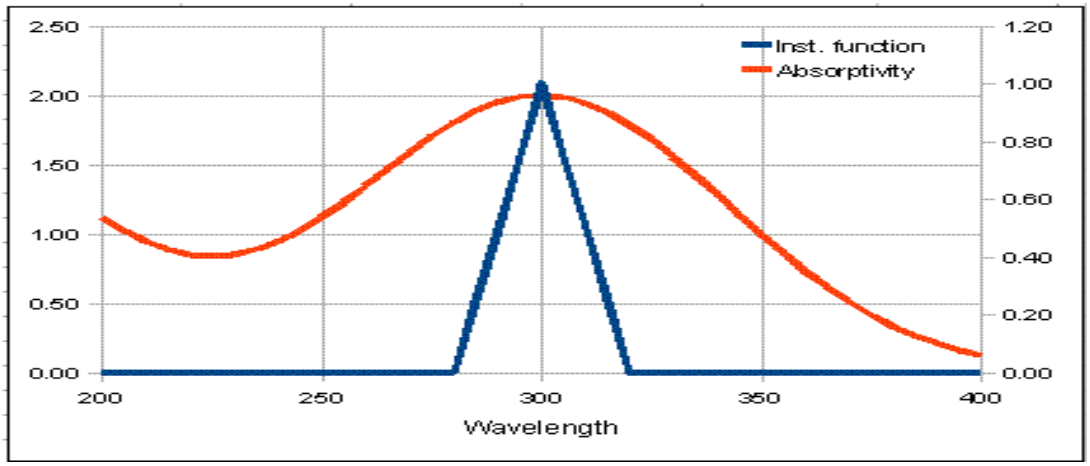

Fig 1: Graph depicting maximum wavelength of absorption (λ_{max})

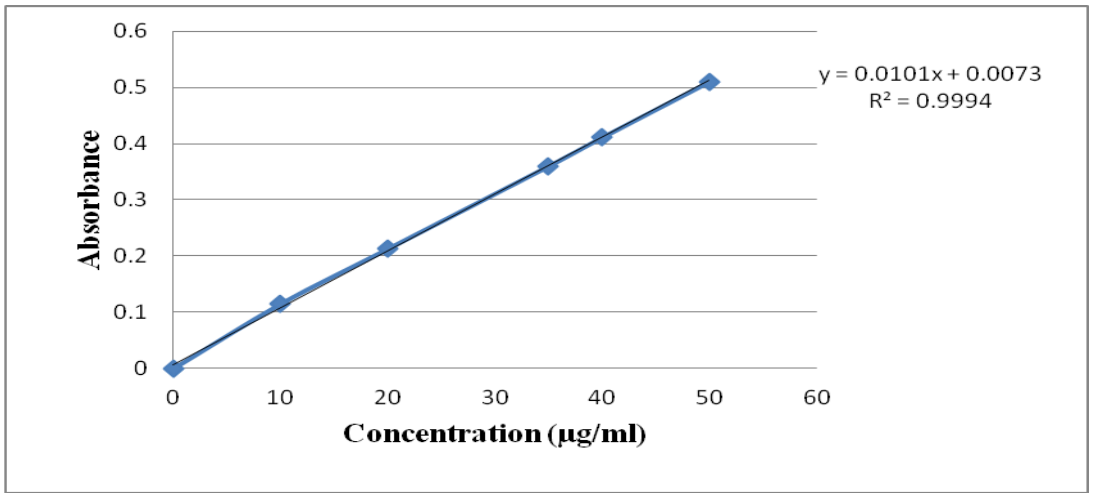

Fig 2: Standard plot of Venlafaxine Hydrochloride

Solubility studies: Weighed quantity of drug (10mg) was suspended in different solvents and shaken using vortex mixer and solubility of drug in different solvents was determined.

Melting point determination: Melting point of drug was determined using Digital Melting point apparatus. The capillary taken was sealed at one end and filled with drug at another end. The capillary was then placed in an apparatus and visual inspection till melting occurred was made and obtained range of temperature was determined.

Partition coefficient determination: The partition coefficient of drug in chloroform:water was determined using separating funnel. Weighed quantity of 20mg of drug was allowed to partitioned between chloroform and water in a separating funnel and finally the concentration of drug present in different phases was determine using UV spectrophotometer.

PC = Log [Concentration of drug in chloroform / Concentration of drug in distilled water]

Micromeritic properties of the blend **[10],[11]**

Angle of repose: The measured weight of 100 gm of the blend was used to determine the angle of repose. Angle of repose was calculated as

$\tan\Theta = h/r$

Where, Θ = angle of repose, h=height, r=radius of the heap.

Bulk density: Apparent bulk density (b) was determined using a graduated cylinder as

$b=M/V$

Tapped density: Tapping of blend for around 5 min and thereafter volume (Vt) occupied and the weight (M) of the blend was measured. The tapped density (t) was:

$t=M/Vt$

Hausner's ratio: Hausner ratio was calculated as dividing t=tapped density by d=bulk density. Thus, flow properties could be determined.

Preparation of placebo of orodispersible tablets **[12]**

The ingredients were passed through #60 sieves. The excipients weighed as required for compression of 10 tablets. Uniform mixing of all ingredients was done leaving magnesium stearate and talc behind. After mixing of others, magnesium stearate and talc were added and mixed in a polythene bag for 5 min. Finally the compression of mixed blend was done using 9mm flat punches on a single punch tablet compression machine. The data of composition of tablet was showed in Table 2.

Evaluation parameters **[13], [14]**

Weight variation: Twenty tablets for determining the average weight was selected and percent deviation from the average was calculated as weight variation.

Hardness: Breaking strength of tablets for approximately ten tablets was determined using Monsanto hardness tester in Kg/cm2.

Friability: Sample of whole tablets corresponding to total 6.5gm was taken and friability was determined using Elite friabilator India. The loss in percentage was calculated as

$\% F = (1-W0/W) \times 100$

Where, W0 is weight of the tablets before the test and W is the weight of the tablets after test.

In Vitro Dispersion time: Dispersion time of ten individual tablets was determined in a beaker containing 0.1 NHCL pH = 1.2

RESULT AND DISCUSSION:

Venlafaxine hydrochloride was observed to be white to off white crystalline powder with no significant

odor. The drug was observed to be absorbed at maximum 300nm wavelength (Figure 1). The standard curve was plotted (Figure 2) with obtained regression value of 0.999. The solubility data (Table 3) showed the drug is freely soluble in phosphate buffer pH 7.4, ethanol and DMSO. The obtained range of melting point was 211-215^{o}C. The determination of partition coefficient of drug showed that drug has lipophilicity (Log P = 4.8). The free solubility in aqueous solution and good lipophilicity of drug allowed the formulation of dosage form that could be easily administered through oral route but the limiting factor of extensive first pass metabolism retard the administration through oral route so at that case preferred route of administration would be sublingual with orodispersion of tablet in the mouth.

Table 3: Solubility data of pure drug

S. No	Solvents	Concentration
1.	Phosphate buffer pH 7.2	14mg/ml
2.	Ethanol	26mg/ml
3.	DMSO	25mg/ml

Precompression parameters of blend of drug and excipients were showed in Table 4. The obtained bulk density 0.73 to 0.75 g/ml, tapped density 0.91-0.95 g/ml indicated that the powder was not bulky but porous in nature. The value of angle of repose (22^{o}-25^{o}) depicted the good flow properties. The good compressibility of the tablet was determined by value of carr's index (13-16).

Table 4: Precompression parameters of Blend of drug and excipients

Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%) ± SD*	Hausner's ratio ± SD*	Angle of Repose ± SD*
FC1	0.74	0.93	15.23 ± 0.041	1.26±0.023	23^{O} 16'±0.45
FC2	0.74	0.91	13.3 ± 0.015	1.14±0.014	23^{O} 45'±0.62
FC3	0.75	0.92	14.24 ± 0.061	1.36±0.046	23^{O} 79'±0.34
FG1	0.75	0.95	14.53 ± 0.032	1.58± .063	23^{O} 56'±0.57
FG2	0.75	0.94	14.64 ± 0.015	1.52±0.053	22^{O} 12'±0.12
FG3	0.75	0.95	14.74 ± 0.045	1.52±0.035	22^{O} 32'±0.53
FK1	0.74	0.94	13.53 ± 0.065	1.17±0.070	23^{O} 47'±0.63
FK2	0.75	0.94	13.63 ± 0.051	1.18±0.019	23^{O} 32'±0.65
FK3	0.74	0.95	14.33 ± 0.072	1.53±0.021	22^{O} 32'±0.54
FS1	0.74	0.92	14.42 ± 0.042	1.14±0.054	24^{O} 15'±0.83
FS2	0.73	0.92	15.32 ± 0.084	1.24±0.031	24^{O} 45'±0.47
FS3	0.73	0.93	13.82 ± 0.041	1.23±0.041	23^{O} 42'±0.41
FM1	0.73	0.91	15.72 ± 0.059	1.24±0.057	25^{O} 74'±0.56
FM2	0.74	0.92	14.03 ± 0.045	1.41±0.053	24^{O} 32'±0.12
FM3	0.73	0.92	14.73 ± 0.074	1.54±0.01	24^{O} 36'±0.34

Table 5: Evaluation parameters of different batches of formulation

Formulation Code	%Weight variation	%Friability	Hardness (Kg/cm^2)	Dispersion Time (sec)
FC1	3.3	0.61	5.1 ± 0.4	40±0.5
FC2	2.1	0.62	5.3 ± 0.8	39±0.2
FC3	3.4	0.76	5.6± 0.09	39±0.6
FG1	4.6	0.43	4.5 ± 0.7	26± 0.1
FG2	5.3	0.52	4.4 ± 0.01	27±0.7
FG3	5.1	0.56	4.7 ± 0.3	25±0.4
FK1	5.4	0.40	4.3 ± 0.09	21±0.7
FK2	5.8	0.43	4.6 ± 0.01	19±0.6
FK3	6.1	0.5	4.8 ± 0.5	19±0.3
FS1	4.1	1.1	3.2 ± 0.1	90±0.7
FS2	4.3	1.2	2.2 ± 0.4	93±0.5
FS3	3.9	1.0	2.4 ± 0.05	92±0.8
FM1	3.3	1.4	1.4 ± 0.07	92±0.7
FM2	3.6	1.5	1.9 ± 0.2	95±0.6
FM3	3.6	1.4	1.6 ± 0.5	94±0.4

The data of evaluation parameters of tablets was showed in Table 5. The obtained range of weight variation of tablet was 2.1-6.1% which falls below the maximum limit of 7.5% as per Indian Pharmacopoeia. The obtained hardness was also within the range and uniform batch to batch for those tablets which were formulated using natural polymers while those which were formulated using synthetic polymers were obtained to be poor in hardness. The 0.5% value of friability showed the good mechanical strength of tablet formulated by natural polymers while tablets formulated using synthetic polymers were failed in friability as value was 1.5%. The range of 19-40 sec. of dispersion of tablets of each batch formulated using natural polymers showed the successful development of orodispersible tablet with the tablets formulated using gum karaya having minimum dispersion time of 19sec. Similarly, tablets formulated using synthetic polymers showed poor orodispersion value of 90-95seconds.

CONCLUSION:

The comparison of hardness, friability and dispersion time of formulations made by synthetic polymers as well as natural polymers showed the efficiency of natural polymers for the development of orodispersible tablets. The gum karaya was observed to be producing best formulations so the final formulations containing drug will be formulated using gum karaya.

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