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Invitro drug release studies of ziprasidone from tablets using natural gums from biosphere

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ABSTRACT

The objective of the present investigation was to found the effect of gums as binders namely acacia, tragacanth, guar gum, gum karaya and gum olibanum on the disintegration, dissolution rate and other qualities of Ziprasidone tablets. Based on dissolution rate (k_1) and dissolution efficiency (DE_{60}) values the order of performance of binders was gum karaya > acacia > gum olibanum > tragacanth > guar gum. Among all gum karaya and acacia gave significantly higher dissolution rate and DE_{60}. Good correlation (r = 0.934) was observed between disintegration times and dissolution characteristics of various tablets.

Key words: Binder, dissolution efficiency, dissolution rate.

INTRODUCTION

Ziprasidone is a novel antipsychotic with high affinity for dopamine D_2 and D_3, serotonin $5HT_{2A}$, $5HT_{2C}$ and $5HT_{1D}$ receptors and high affinity for the $5HT_{1A}$ receptor, where it acts as a potent agonist [1,2]. It is not yet official in any Pharmacopoeia. It is poorly soluble and its aqueous solubility was 21.12mg/l [3]. Its oral absorption is dissolution rate limited. The dissolution rate and bioavailability of poorly soluble drug from solid dosage form depend much on formulation additives. Among the various additives binding agent was found to have significant influence on the dissolution rate of medicament from solid dosage forms [4, 5]. Though Ziprasidone tablets and capsules are available commercially, no work was reported on the pharmaceutical formulation aspects of Ziprasidone. In the present work, the effect of five gums as binders on the dissolution rate of Ziprasidone from tablets was studied.

MATERIAL AND METHODS

Materials:

Ziprasidone (ZPR) obtained as gift sample from Dr. Reddy's laboratories, Hyderabad. Gum olibanum was a gift sample from Girijan Cooperative Ltd., Visakhapatnam. Potato starch, acacia, tragacanth, guar gum, gum karaya, lactose, magnesium stearate and talc were procured from the local market. All other chemical were of analytical grade.

Azona 20 tablets (M/s Sun pharmaceutical industries, J&K, batch no AD81382, Mfg date: June 2008, Exp. Date: May 2010) were procured from local market.

Preparation of tablets:

Compressed tablets of Ziprasidone were prepared by conventional wet granulation method employing five natural gums as binders as per formulae given in Table 1. All the binders were used at 2% concentration of the formula in the form of aqueous solution or mucilage of suitable strength. A 2-5% is the usual concentration range for all the binders used [6]. The damp mass was granulated by passing through mesh no.10 and the granules obtained were dried in an oven at 60^{o}C for 2hrs. The dried granules were again passed through mesh no.16 to break the aggregates. The lubricant and glidant were added to the dry granules and blended. The blend was compressed into tablets on a Cadmach 16 station tablet compression machine to a hardness of 4-5Kg/Sq.cm. The prepared tablets were evaluated for the uniformity of weights, drug content, hardness, friability, disintegration time and dissolution rate.

Table 1: **Formulae of Ziprasidone Tablets Prepared**

INGREDIENT	FORMULATION				
	Z1	Z2	Z3	Z4	Z5
Ziprasidone	20	20	20	20	20
Gum tragacanth	04	-	-	-	-
Guar gum	-	04	-	-	-
Gum karaya	-	-	04	-	-
Gum olibanum	-	-	-	04	-
Acacia	-	-	-	-	04
Lactose	148	148	148	148	148
Potato starch	20	20	20	20	20
Magnesium Stearate	04	04	04	04	04
Talc	04	04	04	04	04
Total weight of tablet (mg)	200	200	200	200	200

Estimation of Ziprasidone:
Ziprasidone content was estimated by UV-Visible spectrophotometric method by measuring absorbance at 319nm in 1% SLS in phosphate buffer pH 7.4. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range of 0-30µg/ml (r=0.999). The excipients used in the formulation did not interfere in the method.

In vitro dissolution studies:
Dissolution rate of Ziprasidone from various tablets was studied using USP XXIII six-station dissolution rate test apparatus (DISSO 2000, LABINDIA) with paddle stirrer. The dissolution rate was studied by placing one tablet containing 20mg Ziprasidone in 900ml of 1% SLS in phosphate buffer of pH 7.4 maintained at 37 ± 0.5^{o}C with a speed of 50rpm. Samples of 5ml were withdrawn different time intervals, filtered (though 0.45µ) and replaced with 5ml of fresh dissolution medium. The samples were suitably diluted and estimated spectrophotometrically at 319nm by using ELICO-167 double beam UV spectrophotometer. The dissolution experiments were conducted in triplicate. From the dissolution data dissolution efficiency (DE_{60}) was calculated as suggested by Khan [7].

Fourier transform infra red spectroscopy
Fourier transform infra red (FTIR) spectroscopy was employed to further characterize the possible interactions between the drug and the gums in the solid state on a Shimadzu FTIR-281 spectrophotometer by the conventional KBr pellet method. The scanning range was 400-4000cm^{-1} and the resolution was 1cm^{-1}.

RESULTS AND DISCUSSION

All the batches of tablets were found to contain Ziprasidone with in 100 ± 5% of labeled claim. Hardness of the tablets of each batch was found to be within 4-5kg/cm^2. All the batches of tablets prepared fulfilled the official uniformity of weight test [8]. The percent weight loss in the friability test was less than 1.0%. All the formulations of Ziprasidone tablets prepared by using different gums as binders like acacia, tragacanth, guar gum, gum karaya and gum olibanum fulfilled the official specification for disintegration time, variations were observed in their disintegration times in the range of 1-5 minutes. The results are shown in Table 2.

Table 2: Evaluation of Various Parameters of Ziprasidone Tablets

Batch no	Hardness kg/ cm^2± SD	Friability (%)± SD	Wt. variation	Drug content (%)± SD	Disnt. Time (min-sec)
Z1	4.9 ± 0.19	0.81 ± 0.24	1.0	99.76±0.14	02.52
Z2	4.3 ± 0.23	0.58 ± 0.18	1.5	98.94±0.21	04.20
Z3	4.1 ± 0.76	0.67 ± 0.09	1.0	99.13±0.09	01.05
Z4	4.5 ± 0.15	0.79 ± 0.16	2.0	98.56±0.23	02.15
Z5	4.6 ± 0.03	0.84 ± 0.56	1.5	99.09±0.04	01.40
C1	4.4 ± 0.98	0.91 ± 0.34	1.0	99.49±0.23	03.10

Dissolution rate of Ziprasidone form the tablets was studied in phosphate buffer pH 7.4 containing 1% SLS as this fluid was found to be suitable dissolution medium with good discriminating power in a separate study [3]. Dissolution profiles of various tablets are shown in Table 3 and in the Figure 1. Dissolution of Ziprasidone from the tablets followed first order

kinetics. The correlation coefficient (r) between log percent undissolved and time was in the range of 0.973-0.997 with various tablet formulations.

Table 3: Dissolution Characteristics of Ziprasidone Tablets Formulated

Batch no	Percent drug released at 3 times (min)			Zero order 'r'	First order 'r'	k_1 (min^{-1})	DE_{60} (%)
	10	30	60				
Z1	34.34	53.18	81.49	0.941	0.995	0.026	64.32
Z2	17.55	42.17	64.24	0.952	0.992	0.014	61.12
Z3	51.34	75.34	93.14	0.816	0.973	0.037	78.5
Z4	39.89	61.45	86.78	0.895	0.987	0.032	70.7
Z5	45.67	65.73	89.78	0.873	0.977	0.037	75
C1	39.62	58.98	85.58	0.941	0.990	0.027	67.34

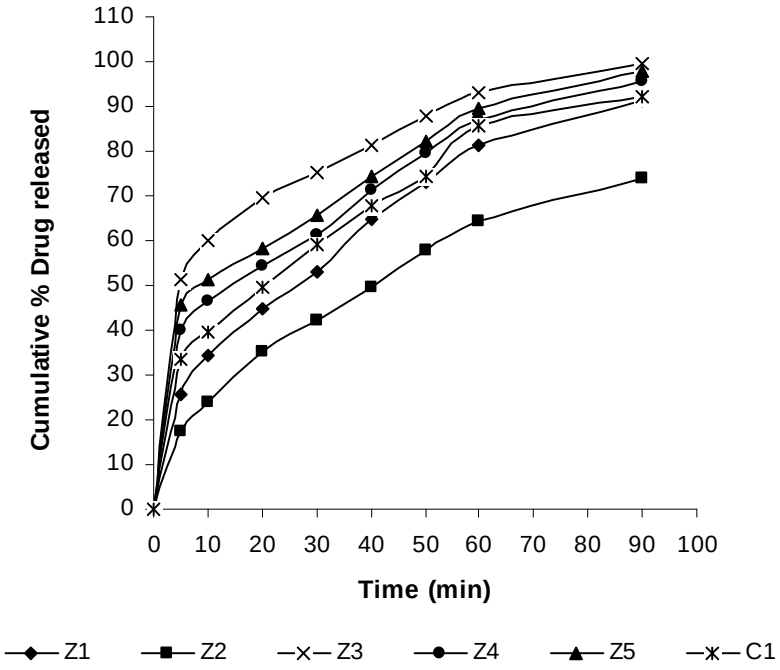
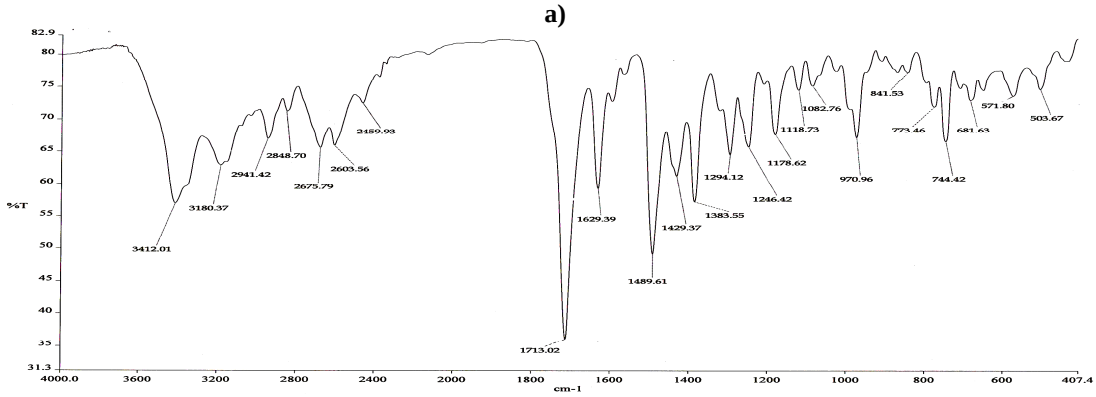


Figure 1: In vitro dissolution profile of Ziprasidone formulations

Much variation was observed in the dissolution characteristics of the tablets formulated with various binders. Based on K_1 and DE_{60} values the order of performance of binders was gum karaya > acacia > gum olibanum > tragacanth > guar gum. Except guar gum and tragacanth, other binders gave good dissolution rates and DE_{60} values compare to the commercial brand. A good correlation was observed between disintegration time and DE_{60} values($r = 0.934$). Hence, the observed difference in the dissolution characteristics of the tablets formulated with various binders is due to the differences in their disintegration and deaggregation properties.

a)


%T
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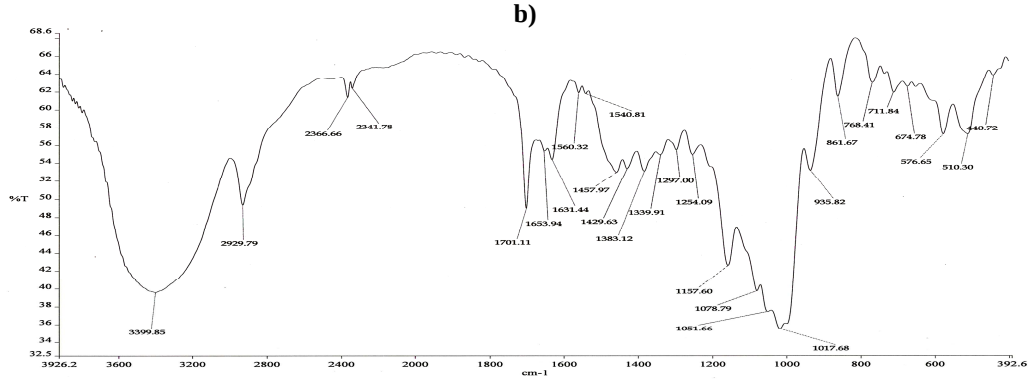
3412.01
3180.37
2941.42
2848.70
2675.79
2603.56
2489.93
1713.02
1629.39
1489.61
1429.37
1383.55
1294.12
1246.42
1178.62
1118.73
1082.76
970.96
841.53
744.42
571.80
503.67

b)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cm-1
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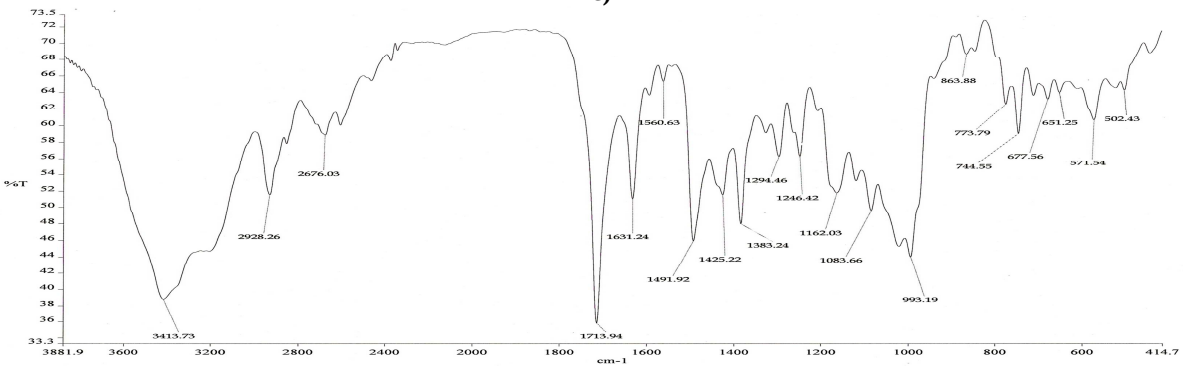
2929.79
2366.66
2341.78
1701.11
1653.94
1631.44
1560.32
1540.81
1457.97
1429.63
1383.12
1339.91
1297.00
1254.09
1157.60
1078.79
1081.66
1017.68
935.82
861.67
768.41
711.84
674.78
576.65
510.30
440.72

c)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2676.03
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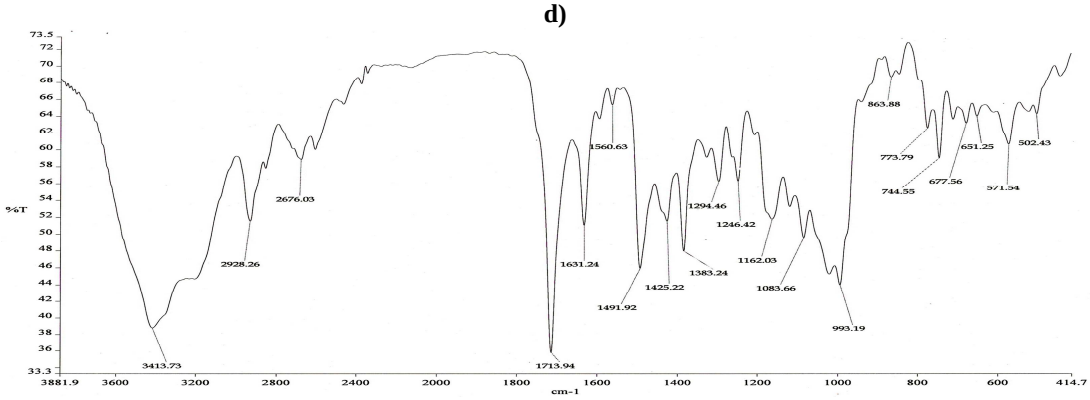
1560.63
1491.92
1425.22
1383.24
1294.46
1246.42
1162.03
1083.66
993.19
863.88
773.79
744.55
677.56
651.25
571.94
502.43

d)


%T
cm-1
3413.73
2928.26
2676.03
1713.94
1631.24
1560.63
1491.92
1425.22
1383.24
1294.46
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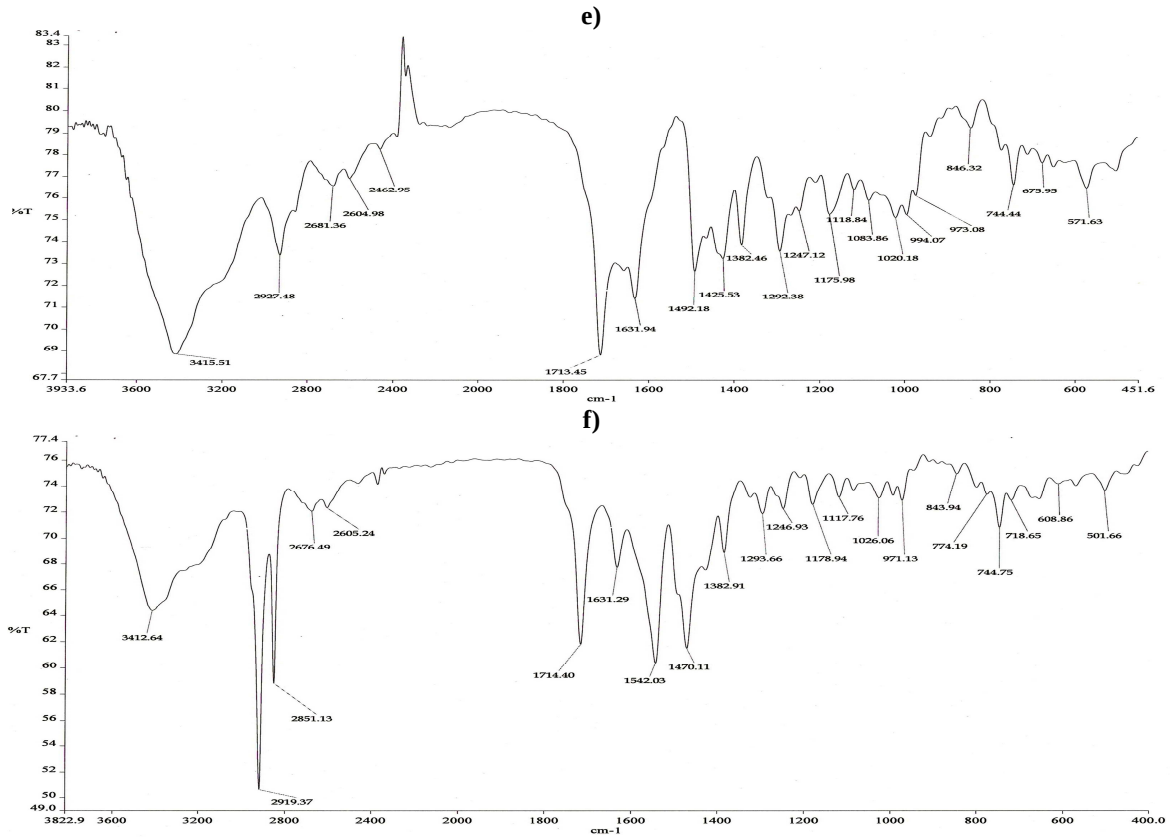

Figure 2: FTIR spectroscopy of a) ZPR b) ZPR + Tragacanth c) ZPR + Gum karaya d) ZPR + Guar gum e) ZPR+ Gum olibanum f) ZPR + Acacia

Figure 2 shows the FTIR spectra of the drug and physical mixture of drug with gums. The principle IR absorption peaks of ZPR at 3412cm^{-1} for NH, 2928cm^{-1} for CH, 1714cm^{-1} for C═O, 1629cm^{-1} for C═N, 1528 for C═C, 1383cm^{-1} for CN and 744cm^{-1} for C-Cl were all observed in the spectra of Ziprasidone as well as in the physical mixtures with gums. Thus, it indicated that the drug is not undergoing any interaction with gums used as binder.

CONCLUSION

The gums are not exhibiting any interaction with ziprasidone. Hence, they can be used as binder in tablet formulation. It was concluded that the type gum as binder significantly affected the *in vitro* drug release. The batch containing 2% gum karaya and 2% acacia as binder shown fast dissolution compare to other binders. Batch containing guar gum shown very slow release compare to commercial batch.

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