

Rapidly disintegrating fast release tablets of diazepam using solid dispersion: development and evaluation

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This study presents development of diazepam tablets, which could provide rapid disintegration and immediate release of drug in oral cavity. Tablets were prepared by conventional wet granulation and direct compression methods. Diazepam was formulated with polyethylene glycol (PEG-6000) as a solid dispersion to increase aqueous solubility and dissolution of drug. Croscarmellose sodium and Aerolac^R were used in tablet formulation to achieve rapid disintegration of tablets prepared respectively by wet granulation and direct compression methods. Tablets developed in this study disintegrated in 37 seconds (wet granulation) and 31 seconds (direct compression) and released 85% in about 21-22 min, whereas marketed tablet disintegrates in 116 seconds and release same amount of drug in 130 min. This study indicates that rapidly disintegrating fast release tablets can be prepared by the conventional methods utilizing the existing infrastructure of tablet manufacturing.

Keywords: Diazepam, Polyethylene-glycol (PEG), Rapidly disintegrating tablets, Solid dispersion

Introduction

Diazepam, a benzodiazepine, is widely used as sedative, anxiolytic and anticonvulsant agent¹ and also very useful in suppressing epileptic convulsion. Rapid termination of epileptic seizure requires rapid absorption of diazepam². Although intravenous therapy is the most rapid way to suppress epileptic convulsions, this route of drug administration, which requires sterile devices and qualified medical personal³ may produce toxic manifestations due to excessive drug concentration^{4,5} and may not be feasible where adequate medical facilities are not available in the immediate vicinity. Alternatively, if diazepam is formulated in rapidly disintegrating fast release tablet dosage form, it could be an alternative to parenteral therapy enabling patient for self-medication even without the aid of water in a situation where onset of convulsion is apprehended. Highly vascularized oromucosal route has been considered as a potential site for drug absorption that provides rapid onset of action^{6,7} and prevents presystemic elimination and fast-pass metabolism of drugs⁸. However, diazepam exhibits poor aqueous solubility that produces erratic and delayed absorption when

administered orally. Rapid absorption of a drug requires rapid dissolution, which in turn depends on higher aqueous solubility.

This study aims to increase aqueous solubility of diazepam and then to formulate such a tablet that disintegrates rapidly and provides rapid dissolution of the drug.

Materials and Methods

Materials

Diazepam (East India Pharmaceutical Works Ltd, Kolkata, India), Aerolac (Pharmaceutical Coatings Pvt Ltd, Mumbai, India), Croscarmellose sodium (Ac-disol), Maize starch, Saccharin-Na (Dey's Medical Stores (Mfg) Ltd, Kolkata, India), Microcrystalline Cellulose (Avicel, PH-102) (Dr Reddy's Laboratory, Hyderabad, India) were obtained as gift samples. Polyethylene glycol-6000 (Qualigen, Mumbai, India), lactose monohydrate (Merc India), magnesium stearate and all other ingredients were obtained commercially and used as received.

Phase Solubility Study

An excess of diazepam was added to stoppered conical flasks containing 10 ml of USP phosphate buffer solution (pH-5.8) and mixtures of phosphate buffer and

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polyethylene glycol (PEG)-6000 (2, 4, 6, 8 and 10% w/v). Flasks were shaken at 50 rpm in shaking incubator (Model KMC 8480 SL, Vision Scientific Company Ltd, Seol, South Korea) at $37\pm0.5^{\circ}\text{C}$ until equilibrium (about 90 h) was reached. The resulting mixtures were filtered and aliquots, following suitable dilutions, were analysed using Spectrophotometer (Genesys, 10 UV, Thermo Electron Corporation, Wisconsin, USA) at 230 nm to determine solubilities of diazepam in different media. Experiments were conducted at constant temperature and in triplicate.

Preparation of Solid Dispersion

Solid dispersion of diazepam and PEG-6000 was prepared⁹. Accurately weighed amount of diazepam and PEG-6000 in different ratios (1:2.5, 1:5 and 1:10) were heated at 134°C in an oil bath with continuous stirring until a homogeneous melt was obtained and then cooled to room temperature. Solid dispersions were stored in vacuum desiccator over fused CaCl_2 for 72 h. Solid dispersions were pulverized with mortar-pestle, sieved through British Standard sieve No.44, dried in vacuum over fused CaCl_2 for 48 h and then stored at room temperature in hermetically sealed glass containers until use.

Preparation of Tablet by Wet Granulation

Raw materials were passed through a No.44 screen. Diazepam (as such or in solid dispersion), microcrystalline cellulose, lactose and intragranular fraction of croscarmellose sodium were mixed and converted into a wet mass with starch paste. Wet mass was then passed through a No.18 screen and resulting granulation were dried in a hot air oven at 40°C for 2 h. Following sieving through No. 22 sieve, granules were mixed with extragranular fraction of croscarmellose sodium and magnesium stearate, and compressed at a constant force into tablets using concave punches (approx.9.5-mm diam) in a 10 station mini press tablet machine (RIMEK, Karnavati Engineering Ltd, Gujarat, India).

Preparation of Tablet by Direct Compression

Diazepam (as such or in solid dispersion) and aerolac were mixed for 10 min and then lubricated with magnesium stearate for 5 min. The powder mixture was compressed into tablets.

Disintegration Test

Disintegration time of tablets was measured using a modified disintegration test method¹⁰. Water (10 ml)

was taken in a petridish and a tablet was carefully placed in the centre and agitated mildly. Time required for complete disintegration of the tablet into fine particles was noted.

Dissolution Test

In vitro release of diazepam from tablets was studied in USP phosphate buffer solution (500 ml, pH 5.8) at $37\pm0.5^{\circ}\text{C}$ and 50 rpm using USP II dissolution test apparatus (model TDP-06P, Electrolab, Mumbai, India). Aliquot (10 ml) was removed from dissolution medium at specified time interval and was replenished immediately with same volume of fresh medium. Aliquot, following suitable dilution, were analyzed spectrophotometrically at 230 nm.

Results and Discussion

Diazepam tablets, prepared by wet granulation method using either diazepam or solid dispersion of the drug in PEG-6000 have following values (Table 1): hardness (measured using Monsanto hardness tester), 3 kg/cm^2 ; friability (determined using Friabilator, Veego, Mumbai, India), 0.05-0.48%; and potency (determined following method of Indian Pharmacopoeia, 1996), $5.09\pm0.04\text{ mg \%}$. Tablets prepared using starch (3.34%) disintegrated in about 25 seconds and released 50% and 85% of the drug in 25 and 128 min respectively (Table 1). Incorporation of croscarmellose sodium (5%) as superdisintegrant decreased disintegration time (12 s). However, no significant change ($P>0.5$) in the time required for 50% ($t_{50\%}$) and 85% ($t_{85\%}$) drug dissolution was noted. On the contrary, increase in croscarmellose-Na concentration increased disintegration time of tablets without producing any appreciable change in drug release.

Croscarmellose-Na is made from sodium carboxymethylcellulose by a cross-linking reaction (esterification), which greatly reduces water solubility of Na-carboxymethylcellulose while permitting material to absorb water and swell many times its weight without losing individual fiber integrity¹¹. However, croscarmellose sodium still contains water-soluble content (6%), which becomes viscous and adhesive when hydrated. When croscarmellose sodium is added to a tablet formulation at higher concentration, absorption of water may cause an increase in viscosity of liquid within tablet and may delay further penetration of water. As water absorption is an important step in disintegration process, increase in croscarmellose sodium concentration showed a delayed tendency in tablet disintegration¹².

Table 1—Composition and physical characteristics of tablets prepared by wet granulation

Ingredients	Amount, mg/tablet							Commercial tablet
	1w	2w	3w	4w	5w	6w	7w	
Diazepam	5	5	5	5	5	5	5	-
PEG-6000	-	-	-	-	12.5	25	50	-
Microcrystalline cellulose	126	126	126	126	126	126	126	-
Lactose	155	140	132.5	125	127.5	115	90	-
Croscarmellose sodium	0	15	22.5	30	15	15	15	-
Starch	10	10	10	10	10	10	10	-
Na-Saccharin	3	3	3	3	3	3	3	-
Magnesium stearate	1	1	1	1	1	1	1	-
Total	300	300	300	300	300	300	300	-
Disintegration time, s	25	12	17	21	37	118	161	116
	(1.79)	(1.83)	(1.17)	(0.81)	(2.06)	(3.27)	(3.77)	(1.88)
t _{50%} , min	25	23	24	25	4.75	4	4	21
	(0.47)	(2.93)	(1.76)	(2.42)	(0.25)	(0.43)	(1.01)	(1.04)
t _{85%} , min	128	128	128.5	126.5	22	16	12.5	130
	(1.76)	(4.73)	(0.79)	(1.29)	(2.08)	(0.76)	(0.58)	(6.18)

Figures in parentheses indicate $\pm$ S.D; n=6 for disintegration time and $\pm$ S.D, n=3 for t_{50%} and t_{85%}

Table 2—Composition and physical characteristics of tablets prepared by direct compression

Ingredients	Amount, mg/tablet				Commercial tablet
	1d	2d	3d	4d	
Diazepam	5	5	5	5	-
PEG-6000	-	12.5	25	50	-
Aerolac	291	278.5	266	241	-
Na-saccharin	3	3	3	3	-
Mg-stearate	1	1	1	1	-
Total	300	300	300	300	-
Disintegration time, s	24	31	101	124	116
	(2.06)	(1.38)	(6.64)	(5.84)	(1.88)
t _{50%} , min	22	7	6	6	21
	(1.0)	(0.29)	(0.87)	(0.50)	(0.76)
t _{85%} , min	125	21	17	13	130
	(4.04)	(0.76)	(0.50)	(0.50)	(6.18)

Figures in parentheses indicate $\pm$ S.D; n=6 for disintegration time and $\pm$ S.D, n=3 for t_{50%} and t_{85%}

Although tablets prepared with starch (3.34%) and croscarmellose-Na (5%) exhibited shortest disintegration time, values of t_{50%} and t_{85%} were high and almost equal to those from the tablets prepared without croscarmellose-Na. Noyeswhitney equations indicate that rate of dissolution is proportional to the aqueous solubility of drugs¹³. Thus prolonged dissolution time could be correlated with poor aqueous solubility of poorly water-soluble drugs. In present study, PEG-6000 (4.17-8.34%) was used to prepare solid dispersion of diazepam. Tablets prepared with solid dispersion of PEG-6000 and drug (2.5:1), disintegrated in 37 s and

released 50% and 85% of drug in 4.75 and 22 min respectively. When the ratio of PEG-6000 and drug in the solid dispersion was increased, disintegration time of tablets also increased, although release of drugs was found to be faster (Table 1). Increase in PEG-6000 is reported¹⁴ to increase disintegration time of a tablet. Faster drug dissolution with increase in PEG-6000 concentration is related with aqueous solubility of the drug. Phase solubility analysis revealed that incorporation of PEG-6000 (0-10%) increased solubility (67-155 mg/l) linearly.

Various mechanisms (reduction of particle size of incorporated drug, partial transformation of crystalline drug to amorphous state, formation of solid solution and complexes, reduction of aggregation and agglomeration, improved wetting of drug and solubilization of drug by the carrier at diffusion layer) are reported¹⁵ responsible for improving aqueous solubility/dissolution properties of solid dispersions. Physico-chemical state of solid dispersion, studied using DSC, X-Ray diffraction & FT-IR, indicated absence of formation of solid solution and complexes; instead a partial transformation of crystalline drug to amorphous state was noted. Partial amorphization together with improved wetting of drug and solubilization of drug by the carrier could be responsible for improvement in solubility and consequent dissolution of the drug. When compared among various formulations, tablets containing PEG-6000:drug (2.5:1) and 5% crosscarmellose-Na were found to be optimum in relation to rapid disintegration and drug dissolution.

Diazepam tablets were also prepared by direct compression method using aerolac as superdisintegrant and either diazepam or solid dispersion of the drug in PEG-6000 in the same ratio as used in wet granulation method. Tablets prepared using diazepam disintegrated in 24 s (Table 2). However, $t_{50\%}$ and $t_{85\%}$ values were found to be 22 and 125 min respectively. Incorporation of drug in solid dispersion (PEG-6000:drug, 2.5:1) marginally increased disintegration time but decreased $t_{50\%}$ and $t_{85\%}$ values considerably. However, further increase in PEG-6000/drug ratio protracted disintegration time of tablets, although rate of drug dissolution became faster. Considering disintegration time of tablets and $t_{50\%}$ and $t_{85\%}$ values, tablets were optimally prepared using solid dispersion of drug in the ratio of PEG/drug at 2.5:1 and 92.84% aerolac. Optimized formulation (5w, 2d), on comparing with a commercial conventional tablet of diazepam, exhibited rapid disintegration and drug dissolution.

Conclusions

Fast dissolving tablet of diazepam can be prepared by existing tablet manufacturing technologies such as wet granulation and direct compression methods using solid dispersion of drug instead of drug as such. Proper selection of drug /carrier ratio and tablet additives can provide rapid tablet disintegration and release of the drug. In present study, use of solid dispersion containing diazepam/PEG-6000 (1:2.5) in the tablets prepared by

either wet granulation or direct compressions disintegrated respectively in 37 s and 31 s and released 85% drug in 22 and 21 min. It is, therefore, proposed that such tablets could be used in emergency treatment of anxiety disorder and effective seizure.

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