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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF DONEPEZIL HYDROCHLORIDE USING MODIFIED POLYSACCHARIDES

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ABSTRACT

The objective of the study was to prepare and evaluate orodispersible tablets of Donepezil Hydrochloride (DPH) using natural modified polysaccharides such as modified karaya gum and modified agar with glycine and mannitol. The prepared formulations were compared with Kyron T-314, a super disintegrant, spray dried lactose, a diluent for improvement in DT and other ODT parameters. FTIR studies revealed no interaction between DPH and excipients. Precompression parameters for all formulations were found to be satisfactory. The oral dispersible tablets formulated using modified agar with glycine showed better disintegration time compared to modified karaya gum formulations. Different concentrations of mannitol and glycine were used in the formulation to study the improvement in the DT. The glycine formulations with modified agar gave better ODT parameters than modified karaya gum with mannitol and glycine formulations. The optimized formulations of modified agar with glycine in different concentrations were prepared with spray dried lactose as diluent and compared with formulations of Kyron T-314 as superdisintegrant with spray dried lactose as diluent. The results of lactose and spray dried lactose as diluents in these formulations did not show any significant difference in ODT evaluation parameters. The formulations were optimized using ODT parameters such as disintegration time, wetting time, water absorption ratio and other physicochemical evaluation parameters. The accelerated stability studies of optimized formulation did not show significant changes compared to initial physicochemical evaluation parameters. To conclude, modified polysaccharides with glycine can be used as superdisintegrant, which may be a cost effective alternative in comparison to synthetic superdisintegrant like Kyron T-314.
Keywords: Orodispersible Tablets, Donepezil Hydrochloride, modified karaya gum and modified agar

INTRODUCTION

Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. However, geriatric and paediatric patients experience difficulty in swallowing conventional tablets, which lead to poor patient compliance. To overcome these problems, scientists developed innovative drug delivery systems known as "Oral Disintegrating Tablets" (ODT). These are novel type of tablets that disintegrate/disperse/dissolve in saliva[1, 2, 3]. The target populations for these oral disintegrating dosage forms have generally been paediatric, geriatric and bedridden or developmentally disabled patients who have dysphagia. Patients with persistent nausea, sudden episodes of allergic attacks or coughing, who are travelling, or who have little or no access to water are also good candidates for oral disintegrable tablets[4]. The benefits in terms of patient compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market. Some drugs are absorbed from the mouth, pharynx and oesophagus when the saliva passes down into the stomach, in such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[5, 6].

ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. Various techniques available for formulating ODTs include freeze drying, sublimation, spray drying, tablet moulding, and melt granulation[7] etc. Despite the different mechanisms involved in these techniques, the aim is to provide the tablet that quickly disintegrate or dissolve upon contact with saliva and also to provide a good mouth feel.

MATERIALS AND METHOD:

Materials:

Donepezil Hydrochloride was obtained as gift sample from RA Chem Pharma Ltd, Hyderabad. Karaya gum, agar and glycine obtained from Yarrow Chem. Products and Kyron T-314 from Corel Pharma Chem Ltd.

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Methods:

Preparation and evaluation of modified karaya gum and modified agar: Modified karaya gum was prepared from tears of karaya gum, were pulverized and then passed through sieve No.100. Ten grams of the powdered gum was taken in a china dish and subjected to heating at 120°C for 2 hours in a hot air oven, and for modified agar the powder was mixed with distilled water and stirred, then kept for swelling. It was kept for three days for drying and ground to pass through sieve No.100. Both the modified gums were evaluated for viscosity (Brookefield viscometer LV DV-II+Pro) and swelling index.

Preparation and evaluation of donepezil hydrochloride oro-dispersible tablets:

Formulation of orodispersible tablets of DPH with glycine & mannitol as excipient:

5mg tablets of total weight 50mg containing 40-60% of glycine and mannitol were prepared but all were found to show poor flow property.

Formulation of orodispersible tablets of DPH with modified karaya gum and modified agar

Table 1: Formulation of ODT of DPH containing modified gums

Formulation	Drug(mg)	Modified karaya gum (mg)	Modified agar (mg)	Lactose (mg)
$DPHMK_1$	5	2.5	-	42
$DPHMK_2$	5	3.75	-	40.75
DPHMK3	5	5	-	39.5
$DPHMA_1$	5	-	2.5	42
$DPHMA_2$	5	-	3.75	40.75
$DPHMA_3$	5	-	5	39.5

Note: All the above formulations of tablets 2% PVPK-30 was added as binder, 0.25mg of Mg.stearate and talc. Total weight of tablet was 50 mg.

Uniformly mixed blend was compressed into tablets containing 5mg drug using 6mm flat face surface punches on a Rimek-1 rotary tablet machine by direct compression method.

Evaluation of oral disintegrable tablets:

Wetting time:

Five circular tissue papers of 10-cm diameter were placed in a petri dish with a 10-cm diameter. 10 ml of water at 37°C±0.5°C containing eosin, a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted.

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wet tablet was weighed.

Water absorption ratio R, was determined using following equation

$$R = W_a - W_b / W_b \times 100 \ldots\ldots\ldots\ldots\ldots\ldots \text{Eq. no.3.8}$$

Where W_a = weight of tablet after absorption

W_b = weight of tablet before absorption

Disintegration time:

Disintegration time was measured using a modified disintegration method. For this purpose, a Petri dish was filled with 10 ml of water at 37°C±0.5°C. The tablet was carefully put in the centre of the petridish and the time for the tablet to completely disintegrate into fine particles was noted.

Assay:

20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 5 mg was weighed and dissolved in 100 ml of 0.1N HCl ml volumetric flask. This dispersion was filtered and 1.2 ml of the above solutions were taken and diluted to 10 ml with 0.1N HCl. The absorbances of this solution were determined at 230 nm against the blank. The percentage assay was calculated from the standard curve.

In-vitro release:

In-vitro drug release of oral disintegrable tablets was determined using USP dissolution apparatus II (Paddle type) (Electrolab TDT-08L). The dissolution test was performed using 900 ml 0.1N HCL at 37°C ± 0.5°C. The speed of rotation of paddle was set at 50 rpm. 5 ml samples were withdrawn at time points of 1, 3, 5, 10, 15, 20 min and same volume was replaced with fresh media. Absorbance of solution was checked by UV spectrophotometer (ELICO- 164 double beam spectrophotometer) at a wavelength of 230 nm and drug release was determined from standard curve.

Formulation of orodispersible tablets using modified polysaccharides with glycine/mannitol[8]

Modified karaya gum/Modified agar was mixed with glycine/mannitolin a glass pestle mortar and triturated for 20 min. The ground mixture was passed through sieve No.22 to get the modified polysaccharides with glycine or mannitol.

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Table 2: Formulation of ODT of DPH containing modified gums with glycine

Formulation	Drug (mg)	Modified karaya gum (10%)	Glycine	Mannitol	Lactose (mg)	Formulation	Drug (mg)	Modified agar (10%)	Glycine	Mannitol	Lactose (mg)
$DPHMKM_1$	5	5	20mg	-	19.5	**$DPHMAM_1$**	5	5	20mg	-	19.5
$DPHMKM_2$	5	5	25mg	-	14.5	**$DPHMAM_2$**	5	5	25mg	-	14.5
$DPHMKM_3$	5	5	30mg	-	9.5	**$DPHMAM_3$**	5	5	30mg	-	9.5
$DPHMKG_1$	5	5	-	20mg	19.5	**$DPHMAG_1$**	5	5	-	20mg	19.5
$DPHMKG_2$	5	5	-	25mg	14.5	**$DPHMAG_2$**	5	5	-	25mg	14.5
$DPHMKG_3$	5	5	-	30mg	9.5	**$DPHMAG_3$**	5	5	-	30mg	9.5

Note: All the above formulations of tablets containing different concentrations and it contain 0.25mg of Mg.stearate and talc. Total weight of tablet is 50 mg.

From these preparations the optimized formulations were formulated with spray dried lactose and with various proportions of Kyron K-314 were prepared

Table 3: Formulation of optimized formulations with spray dried lactose

FORMULATION	Drug(mg)	MKG(mg)	MAG(mg)	Kyron K-314	Spray dried Lactose(mg)
$DPHMKG_2S$	5	30	-	-	14.5
$DPHMKG_3S$	5	35	-	-	9.5
$DPHMAG_2S$	5	-	30	-	14.5
$DPHMAG_3S$	5	-	35	-	9.5
$DPHK_1S$	5	-	-	0.4	44.01
$DPHK_2S$	5	-	-	0.5	44
$DPHK_3S$	5	-	-	0.6	43.9

Note: All the above formulations of tablets containing different concentrations of 0.25mg of Mg. stearate and talc. Total weight of tablet is 50 mg.

Comparative evaluations of optimized modified agar formulations were compared with optimized Kyron-T314 formulations.

Accelerated stability studies:

The optimized formulation was subjected to stability studies at $40^{\circ}C \pm 2^{\circ}C/75\% \pm 2\%RH$ for period of one month. Each tablet was individually wrapped in aluminum foil and packed in ambered colored bottle and put at above specified condition in a heating humidity chamber for one month. The tablets were analyzed for the hardness, disintegration time, and drug content and in-vitro drug release.

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RESULTS AND DISCUSSION:

Evaluation of Orodispersible tablets of DPH using modified karaya gum and modified agar:

Table 4: Post compression parameters of orodispersible tablets of DPH using modified karaya gum and modified agar

Formulation	Weight variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio	Content uniformity (%)	Assay	Q_{20}
DPHMA1	51±1.05	2.5	2.71±0.02	0.22±0.18	30±1.96	35±1.12	132±1.42	99.24±0.58	99.22±0.51	95.67±0.50
DPHMA2	50±0.89	2.5	2.69±0.01	0.25±0.24	25±1.21	27±1.32	135±1.46	99.85±0.86	98.82±0.65	96.90±1.47
DPHMA3	49±0.98	3	2.72±0.04	0.22±0.15	20±1.90	25±1.76	137±1.38	99.62±0.69	99.64±0.54	94.38±1.28
DPHMK1	50±0.98	2	2.71±0.02	0.28±0.21	50±1.24	55±1.57	139±1.26	99.45±0.68	99.02±0.59	94.27±1.26
DPHMK2	50±1.86	2.5	2.69±0.04	0.27±0.16	35±1.52	40±1.43	113±1.81	99.62±0.99	99.26±0.78	95.53±1.64
DPHMK3	52±0.86	3	2.72±0.02	0.27±0.16	25±1.23	30±1.65	123±1.43	99.65±0.79	99.36±0.89	96.78±1.71

From the above results modified agar preparation (DPHMA3) was found to show better DT compared with modified karaya gum preparations but the %release was less.

Evaluation of orodispersible tablets of DPH using modified karaya gum with glycine and mannitol

Table 5: Post compression parameters of orodispersible tablets of DPH using modified karaya gum with glycine and mannitol

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio	Content uniformity (%)	Assay	Q_{20}
$DPHMKM_1$	50±1.19	2	2.77±0.12	0.27±0.12	105±1.21	120±1.29	110±1.23	100.13±0.3	99.87±0.69	95.67±0.50
$DPHMKM_2$	52±1.12	2.5	2.59±.04	0.23±0.18	90±1.96	105±1.57	118±1.29	99.98±0.69	99.82±0.58	95.04±1.47
$DPHMKM_3$	50±0.99	2	2.45±0.01	0.21±0.12	40±1.23	44±1.43	121±1.30	99.80±1.23	99.74±0.46	96.38±1.28
$DPHMKG_1$	51±1.05	2.5	2.71±0.02	0.22±0.18	35±1.24	40±1.57	132±1.42	99.24±0.58	99.74±0.46	96.3±1.26
$DPHMKG_2$	50±0.89	3	2.69±0.01	0.25±0.24	28±1.52	32±1.76	135±1.46	99.85±0.86	98.69±0.97	94.83±1.64
$DPHMKG_3$	49±0.98	3	2.72±0.04	0.22±0.15	22±1.90	28±1.32	137±1.38	99.62±0.69	99.45±0.88	96.28±1.71

From the above formulations modified karaya gum with glycine(DPHMKG3) has shown good DT and %release pattern.

Evaluation of Orodispersible tablets of DPH using modified agar with glycine and mannitol

Table 6: Post compression parameters of orodispersible tablets of DPH using modified agar with glycine and mannitol

Formulation	Weight variation	Hardness (kg/cm^2)	Thickness	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio	Content uniformity (%)	Assay	Q_{20}
$DPHMAG_1$	50±0.98	2.5	2.71±0.02	0.28±0.21	25±1.23	30±1.12	139±1.26	99.45±0.68	99.48±0.56	95.67±0.50
$DPHMAG_2$	50±1.86	2.5	2.69±0.04	0.27±0.16	17±1.24	25±1.32	113±1.81	99.62±0.99	99.85±0.88	95.04±1.47
$DPHMAG_3$	50±0.86	3	2.72±0.02	0.27±0.16	15±1.52	23±1.76	123±1.43	99.65±0.79	99.58±0.88	96.38±1.28
$DPHMAM_1$	50±0.98	2	2.69±0.01	0.28±0.15	25±1.96	35±1.57	113±1.30	99±0.68	99.85±0.98	96.3±1.26
$DPHMAM_2$	49±1.86	2.5	2.71±0.02	0.22±0.21	20±1.90	30±1.43	118±1.29	99±0.99	98.89±0.68	94.83±1.64
$DPHMAM_3$	51±0.89	3	2.72±0.04	0.25±0.16	19±1.52	27±1.65	121±1.23	99±0.79	98.95±0.98	96.28±1.71

From the above, formulations of modified agar with glycine has shown good DT and % release pattern.

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From all the results formulations of DPHMAG2, DPHMAG3, DPHMKG2, and DPHMKG3 were selected and again formulated with spray dried lactose and compared with formulations of Kyron-314.

Table 7: Evaluation of optimized formulations and comparison with formulations of Kyron-314

Formulation	Weight variation(mg)	Hardness (kg/cm^2)	Thicknes (mm)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio	Content uniformity(%)	Assay	Q_{20}
$DPHMKG_2S$	51±1.05	1.5	2.71±0.02	0.22±0.18	25±1.52	30±1.43	132±1.42	99.24±0.58	99.64±0. 86	97.67±0.50
$DPHMKG_3S$	49±0.98	2.5	2.72±0.04	0.22±0.15	20±1.98	30±1.57	137±1.38	99.62±0.69	98.75±0.88	97.38±1.28
$DPHMAG_2S$	50±1.86	3	2.69±0.04	0.27±0.16	15±1.24	25±1.32	113±1.81	99.62±0.99	99.98±0.79	98.97±1.64
$DPHMAG_3S$	50±0.86	2.5	2.72±0.02	0.27±0.16	10±1.52	15±1.76	123±1.43	99.65±0.79	99.94±0.98	99.79±1.71
$DPHK_1S$	50±1.19	2.5	2.77±0.12	0.27±0.12	50±1.21	62±1.21	110±1.23	101.13±0.73	99.99±0.86	94.57±0.50
$DPHK_2S$	52±1.12	3	2.59±.04	0.23±0.18	30±1.96	56±1.92	118±1.29	99.98±0.69	99.88±0.78	95.23±1.47
$DPHK_3S$	52±0.99	3	2.45±0.01	0.21±0.12	25±1.23	44±1.08	121±1.30	99.80±1.23	99.98±0.87	96.57±1.28

The comparative study of optimized formulations of modified agar with glycine and with Kyron T-314 showed better disintegration time of 10 and 15 seconds in comparison to Kyron which produced 25 seconds. The wetting time and water absorption ratio of optimized formulations were also better than synthetic superdisintegrant. All the ODT parameters were found to be better than synthetic superdisintegrant.

DISCUSSION

An attempt has been made to prepare orodispersible tablets of donepezil hydrochloride using modified karaya gum and modified agar with glycine and mannitol. The prepared formulations were compared with Kyron T-314 and spray dried lactose as diluent for improvement in DT and other ODT parameters. The oral dispersible tablets formulated using modified agar with glycine ($DPHMAG_2$, $DPHMAG_3$) showed better disintegration time compared to modified karaya gum formulations. Different concentrations of mannitol and glycine were used in the formulation to study the improvement in the DT. The glycine formulations with modified agar gave better ODT parameters than modified karaya gum with mannitol and glycine formulations. The optimized formulations of modified agar with glycine ($DPHMAG_2$, $DPHMAG_3$) in different concentrations were prepared with spray dried lactose as diluent and compared with formulations of Kyron T-314 ($DPHK_3S$) as superdisintegrant with spray dried lactose as diluent. These formulations ($DPHMAG_2$, $DPHMAG_3$) gave better ODT profiles compared to Kyron formulations ($DPHK_3S$) and results of lactose and spray dried lactose as diluents in these formulations did not show any significant difference in ODT evaluation parameters denoting that lactose can be used as diluent for direct compression of this optimized formulation. To conclude, modified polysaccharides with glycine can be used as superdisintegrant, which may be a cost effective alternative in comparison to synthetic superdisintegrant like Kyron T-314.

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