DESIGN AND EVALUATION OF COST EFFECTIVE ORODISPERSIBLE TABLETS OF DIETHYLCARBAMAZINE CITRATE BY EFFERVESCENT METHOD

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ABSTRACT

Purpose: The aim of the present study was to develop orodispersible tablets of diethylcarbamazine citrate (an anthelmintic) for improving patient compliance, especially, those of paediatric and geriatric categories with difficulties in swallowing, with the prime objective of arriving at cost effective product by effervescent method.
Methods: In the effervescent method mixture of sodium bicarbonate and tartaric acid along with treated agar were used as disintegrants. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, *in vitro* dispersion time.
Results: The tablet formulation containing 16% w/w treated agar, 15% w/w sodium bicarbonate and 15% w/w tartaric acid emerged as the overall best formulation (with an *in vitro* dispersion time of approximately 55 s, $t_{50\%}$ = 9.24 min and $t_{70\%}$ = 18.12 min), based on the *in vitro* drug release characteristics, compared to commercial conventional tablet formulation (which shows 16.48 and 29.24 min respectively for $t_{50\%}$ and $t_{70\%}$). Short-term stability studies (at 40±2°/75±5% relative humidity) on the best formulation indicated that there are no significant changes in drug content and *in vitro* dispersion time ($p<0.05$). IR-spectroscopic studies indicated that there are no drug–excipient interactions.
Conclusions: The present study clearly demonstrates that orodispersible tablets of diethylcarbamazine citrate could be successfully prepared by direct compression method in a cost effective manner employing treated agar. The use of effervescent mixture further assists in taste masking. Undoubtedly the availability of various technologies and the manifold advantages of orodispersible tablets will surely enhance the patient compliance providing rapid onset of action.

Key words: Diethylcarbamazine citrate, orodispersible tablets, effervescent method, treated agar, directly compressible excipient.

1.INTRODUCTION

For the past two decades, there has been an enhanced demand for more patient compliance dosage forms. As a result, the demand for their technologies has been increasing three-fold annually. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are now focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects [1].
Difficulty in swallowing (dysphagia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with those groups [2,3]. Other categories that experience problems in using conventional oral dosage forms include the mentally ill, uncooperative and patients suffering from nausea, motion sickness, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to non-availability of water. These problems led to the development of a novel type of solid oral dosage form called mouth dissolving tablet, which disintegrates/dissolves rapidly in saliva without the need of drinking water.
The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, porous tablets, rapimelts. However, of all the above terms, United States Pharmacopoeia

(USP) approved these dosage forms as orodispersible tablets. Recently, European Pharmacopoeia has used the term "orodispersible tablet" for tablets that disperse readily and within three minutes before swallowing [4]. Upon ingestion, the saliva serves to disperse/ dissolve the dosage form; the saliva containing the dissolved/dispersed medicament is then swallowed in the normal way. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In these cases, the bioavailabilities of drugs are significantly greater than those observed from conventional solid forms such as tablets and capsules [5].
In the present study, orodispersible tablets of diethylcarbamazine citrate (DEC), an anthelmintic [6], were designed using co-processed directly compressible excipient developed in our laboratories (using mannitol and native food grade corn starch) with the prime objective of arriving at a cost effective product. The designed tablets were evaluated for hardness, friability, weight variation, *in vitro* dispersion time, drug content uniformity, *in vitro* dissolution rate (in pH 6.8 phosphate buffer), short term stability and drug excipient interactions (IR spectroscopy).

2.MATERIALS AND METHODS

MATERIALS

Diethylcarbamazine citrate was received as a gift sample from GlaxoSmithKline Pharmaceuticals Ltd., Nashik, Maharashtra. Peppermint flavor (spray-dried) and aspartame were obtained as gifts from Strides Arco Labs Pvt Ltd, Bangalore,India. Sodium bicarbonate, tartaric acid, purified talc, corn starch, D-mannitol and potassium dihydrogen orthophosphate were procured from Sd Fine Chem Limited, Mumbai, India. Sodium hydroxide and sodium lauryl sulphate were procured from Qualigens Fine Chemicals, Mumbai, India. Native corn starch was procured from Manibhadra food products, Hubli, Karnataka, India.

2.1.PREPARATION OF DIRECTLY COMPRESSIBLE EXCIPIENT

The directly compressible excipient developed in our laboratories [7] by co-processing method has been selected for the design and evaluation of cost effective orodispersible tablets of the drug DEC. The directly compressible excipient (DCE) was prepared using a local variety of food grade corn starch (Manibhadra food products, Hubli, Karanataka, India) along with mannitol in 1:1 ratio using 10% w/w starch paste for granulation. The developed excipient was evaluated for hygroscopicity, Carr's index, Hausner's ratio in comparison with the commercial variety of corn starch (SD fine Chem., Mumbai, India), as the control.

Method: All the ingredients were powdered separately in a dry, clean porcelain mortar and passed through # 60 mesh sieve and mixed well in geometrical ratio. Granulating fluid, starch paste (10% w/w) is added to the powder mixture in small quantities, while mixing thoroughly after each addition until a coherent mass was formed. Then it was passed through # 44 mesh sieve and the wet granules were spread on a paper and dried in hot air oven at 55-60^{o} C. The dried granules were then passed through # 36 mesh sieve.

2.2.PREPARATION OF TREATED AGAR

Treated agar (TAG) powders were prepared by taking 10 gm agar powder in distilled water (100 ml) and stirring at 50 rpm with a three- bladed mechanical stirrer for one day. This causes water absorption and swelling. Then the liquid was poured in a large Petri-dish and allowed for drying up to three days in incubator at 37±1^{o} C and then the mass was pulverized and sifted through # 80 mesh sieve [8,9].

2.3.PREPARATION OF ORODISPERSIBLE TABLETS [10]

Orodispersible tablets of DEC were prepared by effervescent method according to the formulae given in Table 1. All the ingredients were passed through # 60 mesh sieve separately. The drug and directly compressible excipient were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Sodium bicarbonate and tartaric acid were pre-heated at a temperature of 80^{o} C for 2 h to remove absorbed/residual moisture and thoroughly mixed in a mortar to get a uniform powder and then added to the above blend. Then the other ingredients were mixed in geometrical order but sodium lauryl sulphate and purified talc were added at the last and mixed for further two minutes. The blend was compressed using 8 mm flat round punches to get tablets of 200 mg weight on 10-station rotary tablet machine (Clit, Ahmedabad, India). A batch of 60 tablets was prepared for all the designed formulations.

Table 1: Composition of orodispersible tablets

Ingredients (mg)/tablet	Formulation Code					
	$TAEM_0$	$TAEM_1$	$TAEM_2$	$TAEM_3$	$TAEM_4$	$TAEM_5$
Diethylcarbamazine citrate	50	50	50	50	50	50
Sodium bicarbonate	24	16	20	24	30	40
Tartaric acid	24	16	20	24	30	40
Aspartame	2	2	2	2	2	2
Sodium lauryl sulfate	2	2	2	2	2	2
Flavour (peppermint)	2	2	2	2	2	2
Purified Talc IP	2	2	2	2	2	2
TAG[a]	-	32	32	32	32	32
DCE[b]	94	78	70	62	50	30
Total weight	200	200	200	200	200	200

[a]TAG- treated agar; [b]DCE- directly compressible excipient

2.4.EVALUATION OF TABLETS

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation [11]. Hardness and friability of the tablets were determined by using Monsanto hardness tester and Roche friabilator respectively. For content uniformity test, ten tablets were weighed and powdered. The powder equivalent to 50 mg of drug was extracted in to distilled water, filtered and the absorbance was measured at 220.2 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was determined as an average of three determinations [12]. For determination of *in vitro* dispersion time, one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5º C and the time required for complete dispersion was determined [13]. IR spectra of the drug and its formulations were obtained by potassium bromide pellet method using Perkin-Elmer FTIR series (model-1615) spectrophotometer in order to rule out drug-carrier interactions.

2.5.*IN VITRO* DISSOLUTION STUDY [14] :

In vitro dissolution of the orodispersible tablets was studied in USP XXIII type-II dissolution test apparatus (Electrolab, model: TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5^{o} C as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 220.2 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of the drug released was calculated and plotted against time.

2.6.STABILITY TESTING

Short-term stability studies on the promising orodispersible tablet formulation ($TAEM_4$) was carried out by storing the tablets at 40 ± 2^{o} / 75 ± 5% RH over a 3 month period. At intervals of one month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time and the results were subjected to statistical analysis using student 't' test.

3.RESULTS AND DISCUSSION

The co-processed directly compressible excipient by wet granulation method was prepared using a local variety of food-grade corn-starch (Manibhadra Food products, Hubli, Karnataka) along with mannitol in 1:1 ratio. This excipient was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and hygroscopicity in comparison with commercial variety of corn-starch (SD Fine Chem. Mumbai), as the control.

Dispersible tablets of DEC were prepared by using the above excipient and evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose (Table 2) and for post compression parameters such as hardness, weight variation, drug content uniformity and *in vitro* dispersion time (Table 3).

Table 2: Pre-compression parameters of DEC formulations

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
$TAEM_0$	0.55	0.64	26.21	14.06	1.16
$TAEM_1$	0.53	0.61	25.74	13.11	1.15
$TAEM_2$	0.50	0.58	24.02	13.79	1.16
$TAEM_3$	0.49	0.56	23.51	12.50	1.14
$TAEM_4$	0.47	0.54	22.68	12.96	1.15
$TAEM_5$	0.46	0.53	21.82	13.20	1.15

The bulk density of pre-compression blends was found to be in the range of 0.46 to 0.55 g/cc, tapped density in the range of 0.53 to 0.64 gm/cc, the Carr's index values were in the range of 12.50 to 14.06%, Hausner's ratio in the range of 1.14 to 1.16 and angle of repose in the range of 21.82 to 26.21.

The hardness of the tablet formulations was found to be in the range of 2.66 to 3.06 kg/cm^2. The friability values were found to be in the range of 0.71 to 1.02%. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits. The percent drug content of all the tablets was found to be in the range of 98.73 to 100.37% of the expected DEC content, which was within the acceptable limits. The results are shown in Table 3.

Table-3: Post compression parameters of DEC orodispersible tablets

Formulation code	Hardness (kg/cm^2)* ± SD	Friability (%)	*In vitro* dispersion time (s)* ± SD	Percent drug content* ± SD	Weight variation
$TAEM_0$	2.66±0.15	1.02	171.66±2.51	98.98±0.81	195-207
$TAEM_1$	2.63±0.15	0.97	91.41±1.18	99.41±1.21	Within the
$TAEM_2$	2.83±0.06	0.92	78.55±0.94	100.37±1.81	IP limits
$TAEM_3$	2.83±0.12	0.82	66.26±1.12	98.73±0.61	(± 7.5%)
$TAEM_4$	2.76±0.15	0.71	54.60±1.23	99.50±0.82	
$TAEM_5$	3.06±0.05	0.73	55.73±0.99	100.03±0.70	

*Average of three determinations; SD- Standard deviation

Among the tablets prepared, formulation $TAEM_4$ containing 16% w/w treated agar, 15% w/w sodium bicarbonate and 15% w/w tartaric acid was found to be promising and has shown an *in vitro* dispersion time of 54.60 s (Fig. 1).

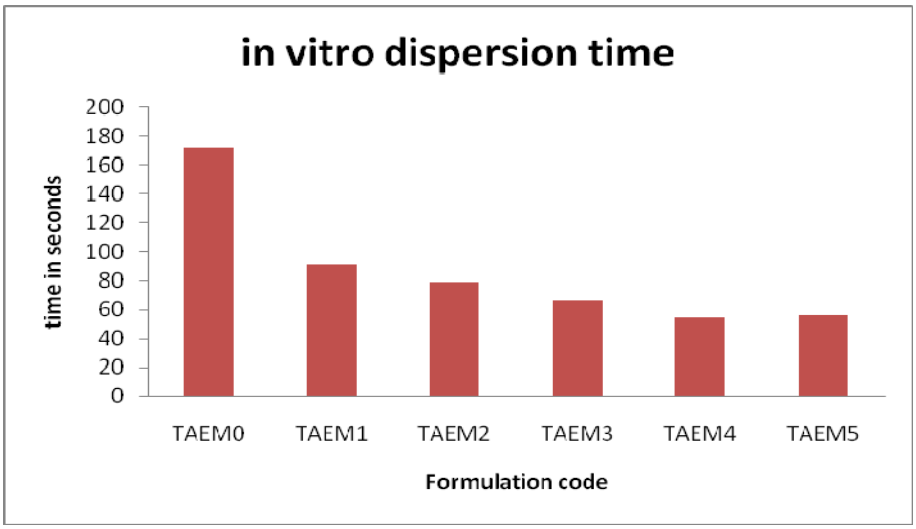

Fig. 1: *In vitro* dispersion time of orodispersible tablets

3.1. *IN VITRO* DRUG RELEASE STUDY

In vitro drug release studies were performed in pH 6.8 phosphate buffer, on the above promising formulation ($TAEM_4$), control ($TAEM_0$) along with commercial conventional tablet formulation (CCF) of the drug. The tablet formulations $TAEM_4$, $TAEM_0$ released 96.70% and 78.27% in 30 minutes compared to commercial conventional tablet formulation (71.51%). The dissolution profiles of the above formulations are depicted in Fig. 2.

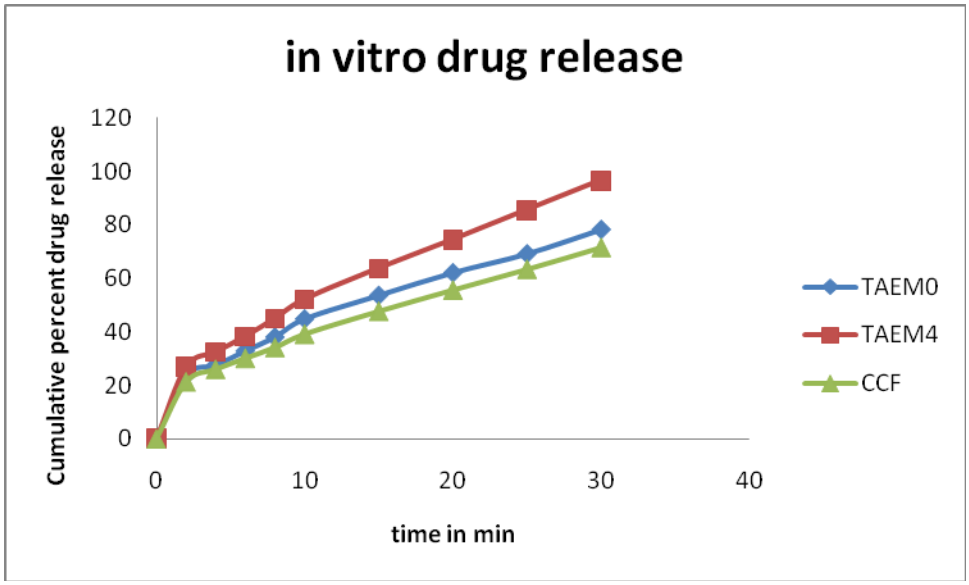

Fig. 2: Comparative cumulative percent drug release vs time plots (Zero Order) of control, promising and commercial conventional tablet formulation in pH 6.8 phosphate buffer

The various *in vitro* dissolution parameter values, viz., percent drug dissolved in 5 min (D_5), 10 min (D_{10}), dissolution efficiency [12] at 10 min (DE_{10min}), $t_{25\%}$, $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ of promising orodispersible tablet formulation in comparison with CCF in pH 6.8 phosphate buffer are shown in Table 4. From this data, it is evident that, $TAEM_4$ formulation displayed nearly two-fold faster drug release compared to CCF, when $t_{25\%}$ and $_{50\%}$ values are considered and has displayed 1.5 fold greater dissolution efficiency, in pH 6.8 phosphate buffer.

Table-4: Comparative *in vitro* dissolution parameters.

Formulation code	D_5 (%)	D_{10} (%)	DE_{10min} (%)	$t_{25\%}$ (min)	$t_{50\%}$ (min)	$t_{70\%}$ (min)	$t_{90\%}$ (min)
$TAEM_0$	30	44.83	27.86	2.36	13.30	25.48	>30
$TAEM_4$	35	52.18	33.12	1.54	9.24	18.12	26.57
CCF	27.5	39.12	24.94	3.42	16.48	29.24	>30

$TAEM_0$ – Control formulation, $TAEM_4$ –promising formulation, CCF- commercial conventional tablet formulation.

D_5-and D_{10} are percent drug release in 5 and 10 min respectively, DE_{10min} is dissolution efficiency at 10 min, $t_{25\%}$, $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are time for 25%, 50%, 70% and 90% drug release respectively.

3.2.DRUG RELEASE KINETICS

The *in vitro* drug release data from the control, promising and the commercial conventional tablet formulations were fitted into two popular models of data treatment: a) cumulative percent drug release versus time (zero-order), b) log cumulative percent drug remaining versus time plots (first-order). When the data was plotted as cumulative percent drug release versus time, the plots obtained show a biphasic release pattern, i.e., a burst release of about 25% drug in the first two minutes followed by zero-order release. Statistical analysis of the data by the method of least squares gives correlation coefficient values in the range of 0.9601 to 0.9631.

3.3. SHORT-TERM STABILITY STUDIES

Short-term stability studies on the above promising formulation (at 40 ± 2^o / 75 ± 5% RH for 3 months) have shown no significant changes in physical appearance, drug content and *in vitro* dispersion time.
Statistical analysis ('t'-test) of drug content data gives 't' value of 2.15 for $TAEM_4$ formulation which is much less compared to the table value of 4.3 ($p<0.05$). There are no appreciable changes in *in vitro* dispersion time up on storage at 40 ± 2^o/ 75 ± 5% RH for 3 months period.
The IR spectrum of the pure drug diethylcarbamazine citrate exhibits characteristic peaks at 3053, 1623, 1408 and 1266 cm^{-1} due to -CH stretching, -C=O stretching, -C-C stretching and CN aromatic stretching respectively. All the above characteristic peaks were found in the IR spectrum of the formulation $TAEM_4$. The presence of above peaks confirms undisturbed structure of drug in the above formulation. Hence, there are no drug-excipient interactions.

4. CONCLUSION

Orodispersible tablets of diethylcarbamazine citrate were successfully prepared by direct compression method in a cost effective manner employing treated agar. The use of effervescent mixture further assists in taste masking. Undoubtedly the availability of various technologies and the manifold advantages of orodispersible tablets will surely enhance the patient compliance (with rapid onset of action, increased bioavailability, good stability) and its popularity in the near future.

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