



DESIGNING OF COLON SPECIFIC MATRIX TABLET OF DIETHYL CARBAMAZINE CITRATE FOR THE TREATMENT OF FILARIASIS

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ABSTRACT

The main aim of the study was to develop colon specific sustained release matrix tablets of diethyl carbamazine citrate (DEC), an anthelmintic for improving patient compliance, delivered to colon for its effective actions. The colon targeted matrix tablet was prepared by wet granulation technique using different percentage of guar gum as matrix carrier and coated with Eudragit L 100. Seven batches of matrix tablets were prepared with varying percentage of guar gum and hydroxyl propyl methyl cellulose (HPMC). The dissolution study of DEC matrix tablet in simulated colonic fluid (phosphate buffer pH 6.8) was 96.78% at the end of 24hr study. The best result of studies showed that colon targeted matrix tablet containing 48% guar gum was most to provide targeting of DEC for local action in the colon. Short term stability studies (at 40±2°C/75±5% RH for 3 months) on the best formulation indicated that there no significant changes in drug content. IR spectroscopic study indicated that there are no drug excipient interactions.

KEYWORDS: Diethyl carbamazine citrate, Colon specific sustained release matrix tablets, IR spectroscopy, Guar gum

INTRODUCTION

Recent advances in Novel Drug Delivery Systems (NDDS) aim for designing dosage forms, convenient to be manufactured and administered, free of side effects, offering immediate release and enhanced bioavailability, so as to achieve better patient compliance. These delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are need most, and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the GIT, namely stomach and small intestine¹. Colon targeted drug delivery^{2,3} would ensures direct treatment at the disease site, lower dosing and less systemic side effects. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. For example, molecules that are degraded/poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more benign environment of the colon. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery. Colon-specific drug delivery⁴ system is considered to be beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease⁵ e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted). A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the

colon. Hence the choice of drug DEC for filariasis was based not only on its efficacy, but also on lack of side effect, ease of administration of single dose and low cost. The development of resistance may not be a problem in clinical use of anthelmintics⁶. The drug should be delivered to colon for its effective action against microfilariae. The administration of drug colon specific sustained release matrix tablets dosage form to provide maximum amount of DEC for location in colon still resulting in relief of filariasis without systemic side effect^{7,8}.

MATERIALS AND METHODS

Diethyl carbamazine citrate was received as a gift sample from Veeco labs pharmaceutical Ltd., Medchal, A.P. Guar gum and HPMC were obtained as gifts from Aurobindo labs Pvt Ltd, A.P. Citric acid, Purified Talc, Starch and methanol were procured from SD fine chem. Ltd Mumbai.

PREPARATION OF ORODISPERSIBLE TABLETS

Matrix tablet of DEC was prepared by wet granulation method using 10% starch paste. Accurately weighed quantities of ingredients mentioned in the above table were passed through sieve no. #30 and lubricant and glidant were passed sieve no. #80. All the ingredients except lubricant (mg.stearate), Glidant (talc) were manually blended homogenously in a mortar by a way of geometric dilution. The mixture was moistened with aqueous solution and granulated through sieve no. #30 and dried in a hot air oven at 60°C for sufficient (3-4 hrs) so that the moisture content of granules reached 2-4 %. The dried granules were passed through sieve no. #30 and blended with talc and mg. stearate. The homogenous blend was then compressed into tablets (230mg each) using deep concave punch. The compression force was adjusted to give tablets with approximately 6.5kg /sq.in hardness on Monsanto tablet hardness tester.

TABLE-I COMPOSITION OF COLON SPECIFIC MATRIX TABLET

Ingredients	Formulation design of tablets						
	CSM ₁	CSM ₂	CSM ₃	CSM ₄	CSM ₅	CSM ₆	CSM ₇
DEC (mg)	10	10	10	10	10	10	10
Guar gum(mg)	28	46	65	83	102	111	123
HPMC (mg)	134	126	97	79	60	51	49
Starch (mg)	22	22	22	22	22	22	22
Citric acid (mg)	22	22	22	22	22	22	22
Mg. stearate (mg)	4	4	4	4	4	4	4
Talc(mg)	10	10	10	10	10	10	10
Total(mg)	230	230	230	230	230	230	230

TABLE II-COMPOSITION OF COATING SOLUTION

Ingredients	Coating composition						
	CSM ₁	CSM ₂	CSM ₃	CSM ₄	CSM ₅	CSM ₆	CSM ₇
Eudragit RL-100	10 %w/v	10% w/v	10% w/v	10%w/v	10% w/v	10% w/v	10% w/v
PEG4000 (1% w/v)	1% w/v	1% w/v	1% w/v	1% w/v	1% w/v	1% w/v	1% w/v

EVALUATION OF GRANULES:

ANGLE OF REPOSE

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Therefore, $\theta = \tan^{-1} h/r$

Where θ = angle of repose.

h = height of the cone in cm.

r = radius of the cone base in cm.

BULK DENSITY (ρ_b)

An accurately weighed quantity of granules of powder from each formula previously lightly shaken to break any agglomerates formed was introduced into a 250 ml measuring cylinder. After the initial volume was observed. The bulk density was calculated by using the following formula

$$\text{Bulk density } (\rho_b) = \text{weight of the powder (W)}/\text{bulk volume of the powder}(V_b)$$

TAPPED DENSITY

An accurately weighed quantity of granules(W) was carefully transferred into 250 ml measuring cylinder. The cylinder is then allowed to tap on to a wooden surface from the height of 2.5 cm at one second intervals. The tapping was continued until no further change in volume was obtained (V_t).The tapped density is calculated by the following formula.

$$\text{Tapped Density } (\rho_t) = \text{Mass of the granules (W)}/\text{Tapped volume of the granules}(V_t)$$

Hausner's Ratio :The Hausner's ratio is calculated by the following formula

$$\text{Hausner's Ratio} = \text{Tapped } (\rho_t) / \text{Bulk}(\rho_b) \times 100$$

TABLE II-VALUE OF HAUSNER'S RATIO

Ratio	Type
<1.25	Good
>1.25	Poor

COMPRESSIBILITY INDEX

The compressibility index of the granules was determined By Carr's compressibility index

$$\text{Carr's index \%} = (\rho_t - \rho_b) / \rho_t \times 100$$

Where, ρ_t is the tapped density of the granules.

ρ_b is the bulk density of the granules

EVALUATION OF TABLETS

THICKNESS

The thickness of six tablets was measured using vernier calipers. The extent to which the thickness of each tablet deviated from $\pm 5\%$ of the standard value was determined.

HARDNESS

Monsanto hardness tester determined hardness of the tablets. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded

FRIABILITY

Friability of tablets was performed in a Roche friabilator. Ten tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed. The percentage of friability can be calculated by

$$\% \text{Friability} = (WI-WF)/WI \times 100$$

Where WI is initial weight of tablet

WF is after evolution the weight of tablet

WEIGHT VARIATION TEST

Uniformity of weight test as described in the IP was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation.

UNIFORMITY OF DRUG CONTENT

Drug content for DEC tablet was done by the assay method. First the prepared tablet (10mg API) was crushed and added to 10ml of methanol. After 30 minutes the solution was filtered, from that 1ml solution was withdrawn and diluted up to 50ml which was the stock solution. From the stock solution 4ml was withdrawn and diluted up to 10ml getting desired concentration of 8 μ g/ml. From the desired concentration, the drug content of formulations were

calculated using calibrated standard curve equation $y=0.0069x-0.0002$.

INVITRO DISSOLUTION STUDY

The in vitro drug release study was performed by using the dissolution apparatus USP-I type (Basket type) at rpm speed 100 for 2 hr in 0.1 N HCL(900 ml).Then the dissolution medium was replaced with pH 7.4 Phosphate buffer(900 ml) and tested for 3 hr as the average transit time of small intestine 3 hr. After 5 hr, the dissolution medium was replaced with ph 6.8 phosphate buffer and tested for next 19 hr. At the end of the period 10 ml of sample was taken and analysed for Diethyl carbamazine content as described previously. At 10 ml fresh and filtered dissolution medium(buffers) was added to make the volume after the each sample withdrawal.

STATISTICAL ANALYSIS

Except dissolution all evaluation parameters were expressed as mean ± standard deviation.

STABILITY STUDIES

Short term stability studies on the above promising formulation (at $40\pm 2^{\circ}\text{C}/75\pm 5\%$ RH for 3 months) have shown no significance changes in physical appearance and drug content.

FTIR STUDY

IR spectroscopy is one of the important analytical technique for functional group identification for chemicals. The drug polymer interaction was studied by FTIR spectroscopy.IR spectra of drug and its formulations were obtained by KBR pellet method.

RESULTS AND DISCUSSION

Colon specific matrix tablets of DEC were prepared by using the above excipient and evaluated for pre-compression parameters such as bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose (Table IV) and for post compression parameters such as hardness, thickness, weight variation, drug content uniformity and friability (Table V).

TABLE IV: PRE-COMPRESSION PARAMETERS OF DEC FORMULATIONS

Formulation Code	Bulk Density(g/cc)	Tapped Density(g/cc)	Angle of Repose(θ)	Carr's Index($\%$)±S.D	Hausner's Ratio
CSM1	0.57±0.06	0.64±0.05	26.27±0.98	12.28±0.01	1.12281±0.03
CSM2	0.58±0.06	0.66±0.01	28.36±0.89	12.12±0.03	1.13793±0.02
CSM3	0.58±0.03	0.67±0.03	28.42±1.06	13.43±0.02	1.15517±0.02
CSM4	0.59±0.04	0.69±0.03	25.42±1.03	14.49±0.01	1.16979±0.04
CSM5	0.63±0.02	0.71±0.02	24.97±0.93	11.26±0.03	1.12698.0.03
CSM6	0.65±0.03	0.73±0.04	24.73±1.08	10.95±0.05	1.12308±0.02

TABLE V POST-COMPRESSION PARAMETERS OF DEC TABLETS

Formulation code	Hardness (Kg/sq.in)±S.D	% Friability ±S.D	% DC±S.D	Avg tab.wt±S.D	Thickness±S.D (mm)
CSM1	6.9±0.114	0.58±0.01	96.92±0.81	230.2±0.02	4.1±0.1
CSM2	6.8±0.118	0.88±0.03	97±0.91	230±0.03	4±0.2
CSM3	6.8±0.152	0.94±0.08	97.25±0.70	230.2±0.03	4±0.9
CSM4	7.1±0.155	0.52±0.01	97.375±0.65	230±0.02	4±0.01
CSM5	6.9±0.153	0.67±0.02	97.645±0.71	230.1±0.02	4±0.01
CSM6	7±0.110	0.79±0.06	97.826±0.83	230.1±0.07	4±0.01
CSM7	7.2±0.113	0.85±0.01	98.007±0.84	230±0.9	4±0.001

The bulk density of pre-compression blends was found to be in the range of 0.57 to 0.654gm/cc, tapped density in the range of 0.64to 0.73 gm/cc, the Carr's index values were in the range of 10.95 to 14.49% ,angle of repose in the range of 24.73 to 28.42 and Hausner's ratio in range of 1.122to1.169,. The hardness of the tablet formulations was found to be in the range of 6.8to 7.2 kg/cm². The friability values were found to be in the range of 0.52 to 0.94%. 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 96.92 to 98.007% of the expected DEC content, which was within the acceptable limits. The results are shown in Table V

DRUG CONTENT

The % age of drug content is obtained by the fixing the concentration (8µg/ml) of the slandered curve using the equation $y=0.0069x-0.0002$

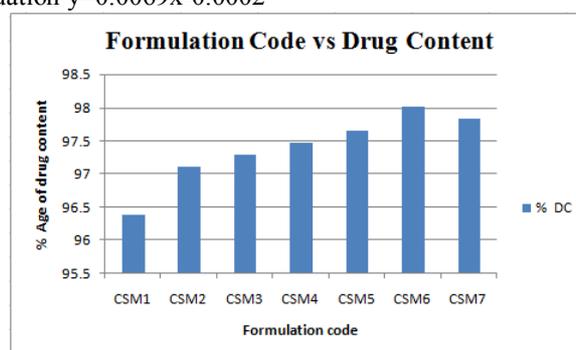


Fig. I: DRUG CONTENT OF FORMULATION CODES.

IN VITRO DRUG RELEASE STUDY

In vitro drug release studies were performed in pH 6.8 phosphate buffer, on the above promising formulation (CSM6) gives maximum amount of drug release comparing to other formulations. The percentage of drug release of CSM6 is best giving 96.78% which contains 48% of guar gum. CSM7 formulation contains 54% of guar gum giving 87.65%. The in vitro dissolution study was shown by CSM1 containing 12% of guar gum (95.47%), CSM2 containing 20% guar gum (96.78%), CSM3 containing 28% guar gum (94.17%) were failed to target the DEC in colon because these formulation release the drug within 16hrs, CSM4 containing 36% guar gum (94.17%) and CSM5 containing 44% guar gum (95.47%) but less than the release of CSM6 formulation. The dissolution profiles of the above formulations are depicted in figure II.

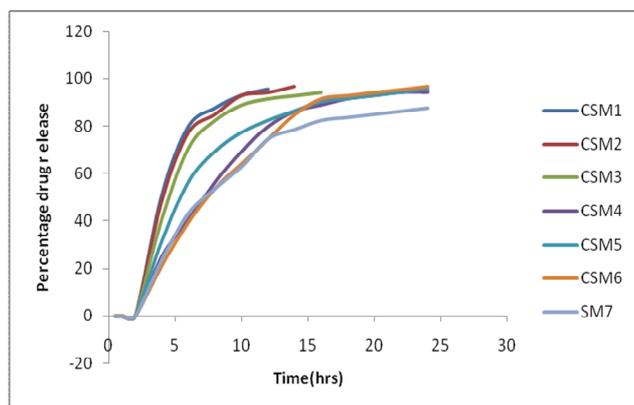


Fig. II: COMPARATIVE DRUG RELEASE STUDY VS TIME PLOTS.

SHORT-TERM STABILITY STUDIES

Short-term stability studies on the above promising formulation (at $40 \pm 2^\circ$ / $75 \pm 5\%$ 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 2.17 for ORD6 formulation which is much less compared to the table value of 4.3 ($p < 0.05$). The IR spectrum of the pure drug diethyl carbamazine 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 CSM6. The presence of above peaks confirms undisturbed structure of drug in the above formulation. Hence, there are no drug-excipient interactions.

CONCLUSION

A Colon specific based drug delivery system can be designed for controlled release of DEC using HPMC and Guar gum as carrier. Here the guar gum is used as carrier and delays the release of drug for prolonged time period. It was evident from the results that rate of drug release can be controlled through carrier of the core. From the developed formulations the release of DEC was best in CSM₆ formulation i.e. (in-vitro study). From the FTIR study, it was confirmed that the drug & excipients in the formulations were compatible with each other.

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