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FORMULATION, EVALUATION AND OPTIMIZATION OF ORODISPERSIBLE TABLET CONTAINING ANTI-EMETIC DRUG

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Abstract:

Prochlorperazine Maleate is a dopamine (D_2) receptor antagonist that belongs to the phenothiazine class of antipsychotic agents that are used for the antiemetic treatment of nausea and vertigo. In current study an attempt was made to prepare Orodispersible tablet of Prochlorperazine Maleate using Ac-di-sol, sodium starch glycolate and crospovidone as oral taste masking agent.

Mass extrusion technique was used for preparing granules. Tablet was formulated with three super disintegrants e.g. sodium starch glycolate, crosscarmellose sodium and crospovidone. Blend was examined for bulk density, angle of repose, tapped density and hausner's ratio.

Formulated tablets were evaluated for drug content, hardness and friability and disintegration time. Oral cavity disintegration time was found to be 22 sec. Sublimation method prepared tablets were used as reference standard by using camphor. Tablets prepared by using superdisintegrants had less disintegration time than those prepared by sublimation method.

Keywords: Orodispersible, Prochlorperazine Maleate, Super disintegrating agents.

Introduction

Oral route of administration still continues to hold the most preferred route drug administration due to its various advantages including ease of ingestion, avoidance of pain during administration, versatile formulation and most importantly patient compliance. Most popular solid dosage forms are tablet and capsule. Solid dosage forms that can be disintegrated dissolved, or suspended by saliva in the mouth resulting in easy of swallowing can provide significant benefits to pediatric and geriatric population, as well as other patients who prefer the convenience of

easily swallow-able dosage forms. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva[1].

Taste masking is an essential requirement for fast dissolving tablets because most drugs possess the bitter taste. Taste masking of the active ingredients can be achieved by various techniques[2]. Two approaches are commonly utilized to overcome bad taste of the drugs. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor[3].

Taste masked granulesof bitter drugs can be prepared by using Ac-di-sol, sodium starch glycolate and crospovidone and ethanol. The extrusion technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. The process involves embedding a drug in a polymeric carrier while shaping the composite material to form a pharmaceutical product[4].

In the present study an attempt was made to prepare taste masked granules of Prochlorperazine Maleate. Taste masking of Prochlorperazine Maleate was carried out by using Eudragit E 100 (Mass extrusion method). These taste masked granules or complex was further formulated into the mouth-dissolving tablet by direct compression method using sodium starch glycolate, cross carmellose sodium and crospovidone as the super-disintegrants.

Materials and Methods

Prochlorperazine Maleate was obtained as a gift sample from Unichem Pvt. Ltd. Mumbai. Sodium starch glycolate, cross carmellose sodium, crospovidone and Ac-di-sol, sodium starch glycolate and crospovidone were obtained as gift samples from Blue Cross Pvt. Ltd. Nashik.

Formulations of drug-Ac-di-sol, sodium starch glycolate and crospovidone loaded granules were prepared by mass extrusion technique[4]:

Drug quantity were kept fixed and mixed with different amount of powdered Ac-di-sol, sodium starch glycolate and crospovidone i.e. at 1:1, 1:2, 1:3 and 1:4 ratios with the help of mortar and pestle, then ethanol 10% V/V was added to each mixture. Gel was prepared using the mixture of the drug and Ac-di-sol, sodium starch glycolate and crospovidone which was converted into the taste-masked granules by the extrusion method. The gel was prepared manually by extruded or pressed out using a syringe, then ethanol was removed by evaporation from the granules by overnight and subsequently the solidified string shaped gel was crushed into granules using a mortar and pestle.

Selection of drug-superdisintegrants ratios:

Four batches were prepared containing drug with superdisintegrants (Ac-di-sol, sodium starch glycolate and crospovidone) in the ratio of 1:1, 1:2, 1:3& 1:4 in ethanol by the above-mentioned method. On the basis of the taste of thegranules ratio 1:3 was finalized for further study.

Physical evaluation of drug- superdisintegrants granules:

Granules were evaluated for angle of repose, bulk density, tapped density, Hausner's ratio.

Formulation of [bitter less] fast dissolving tablet of drug: **superdisintegrants granules by disintegrant addition method.**

Fast dissolving tablets of Prochlorperazine Maleate: Ac-di-sol, sodium starch glycolate and crospovidone granules were prepared using direct compression method after incorporating different superdisintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate indifferent concentrations. Mannitol, Avicel PH 101 was used as directly compressible diluents. Nine formulations of Prochlorperazine Maleate: Ac-di-sol, sodium starch glycolate and crospovidone granules were prepared and each formulation contained one of the three disintegrant in different concentration. Tablet weight was 125 mg; 8 mm punch was used for compression. Ingredient are depicted in table no. 1

Table 1: Formulation table of batch B1-B9.

Ingredient mg	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**
Granules (≡4mg Prochlorperazine)	18.18	18.18	18.18	18.18	18.18	18.18	18.18	18.18	18.18
Mannitol	70	70	70	70	70	70	70	70	70
Avicel pH 101	30.58	29.33	28.08	30.58	29.33	28.08	30.58	29.33	28.08
Crosscamellose Sodium [Ac Di Sol]	2.50	3.75	5.00	-	-	-	-	-	-
Sodium starch Glycolate	-	-	-	2.50	3.75	5.00	-	-	-

Crospovidone	-	-	-	-	-	-	2.50	3.75	5.00
Aerosil	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62
Aspartame	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tablet weight	125	125	125	125	125	125	125	125	125

Evaluation of formulated tablet

Tablet Hardness[5]

The strength of tablet is expressed as tensile strength (Kg/cm2). The tablet crushing load, which is the force required to break a tablet into halves by compression .It was measured using a tablet hardness tester (Pfizer Hardness Tester).

Weight Variation Test[5]

Weight variation test was done by weighing 20 tablets individually; calculating the average weight and comparing the individual tablet weight to the average.

Friability[5]

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the Purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weigh.

Content Uniformity[7]

Total 5 tablets were powdered and the blend equivalent to 4 mg of Prochlorperazine Maleate was weight and dissolved in appropriate quantity of pH 1.2 solutions. Solution was filtered, diluted and drug content was analyzed by spectrophotometrically.

Disintegration Time[5]

The disintegration time of tablet was measured in water (37^0C) according to USP disintegration test apparatus.

Wetting Time[6]

Yunixia et.al reported method was followed to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small petry dish (ID6.5cm) containing 6ml of pH 6.8 (simulated saliva fluid). A tablet was put on the

paper and the time for complete wetting was measured. Three subsequent trials for each were performed data are revealed in table no. 2

***In-Vitro* Release Profile of Formulated Tablets**

The dissolution of Prochlorperazine Maleate tablets was carried out in basket type dissolution apparatus. The dissolution medium was 900 ml of gastric simulated fluid (without enzyme) pH 1.2 maintained at 37^0C+ 10 C. The basket was rotated at 50 rpm for 20 min. The sample of 10 ml was withdrawn after every 5 min. and its absorbance was measured at 254nm**.**

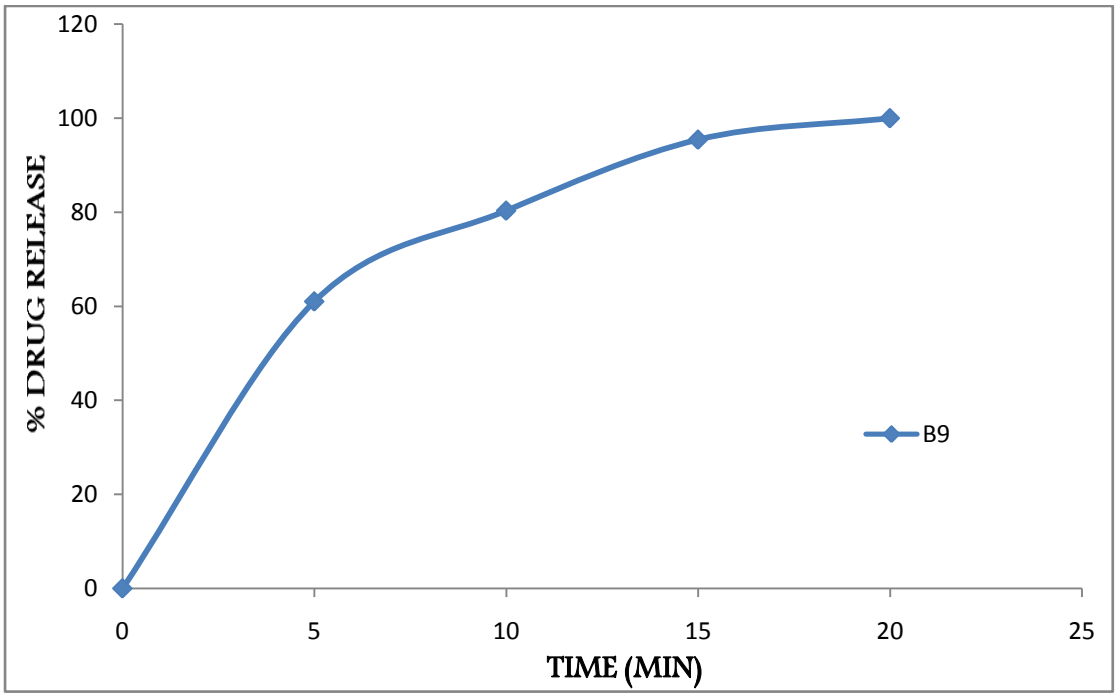
Table 2: Evaluation of batch B1-B9 and C1-C3.

Formulation	**Hardness (Kg/Cm^2) ±SD**	**Friability (%)**	**Wetting time (sec) ±SD**	**Thickness (mm) ±SD**	**Drug content %**	**Disintegration Time (sec)**
B1	3.13±0.005	0.44	46.66±0.03	2.24±0.01	99.95	30.33±0.01
B2	3.46 ±0.01	0.28	39.66±0.02	2.22±0.01	99.00	20.66±0.01
B3	4.0±0.01	0.2	22.66±0.05	2.2±0.02	101.21	10.66±0.02
B4	3.76±0.005	0.48	40.66±0.03	2.21±0.05	100.5	20.66±0.005
B5	3.96±0.01	0.36	36.33±0.05	2.22±0.02	100.07	16.0±0.02
B6	4.03±0.01	0.28	22.00±0.01	2.21±0.01	98.95	12.22±0.01
B7	3.96±0.01	0.52	43.33±0.06	2.22±0.03	99.9	23.66±0.01
B8	4.03±0.01	0.24	34.33±0.05	2.20±0.005	100.12	15.66±0.005
B9	4.06±0.005	0.16	19.66±0.06	2.19±0.01	101.1	10.33±0.01
C1	4.4±0.01	0.15	3.15±0.06 min	2.21±0.005	99.95	2.35±0.01
C2	3.1±0.005	1.96	2.20±0.05 min	2.24±0.01	100.25	1.68±0.02
C3	3.4±0.01	0.96	2.0±0.05 min	2.22±0.03	100.12	1.31±0.02

Optimization of Formula

From the above formulations the optimized formula from Drug: Ac-di-sol, sodium starch glycolate and crospovidone granules; tablets was selected, depending upon the several factors such as less disintegrant concentration, less disintegration time and fast dissolution rate figure no. 1

Figure No. 1: Dissolution profile of batch B9 (disintegrant addition method).



Stability Studies

The stability studies of formulated tablets were carried out at 40^0C and 75% RH[10] using a stability chamber for one month. The effects of temperature and time on the physical characteristics of the tablet were evaluated for the assessment of formulations stability. The different parameters that were studied are drug content, disintegration time, hardness, friability, and dissolution rate.

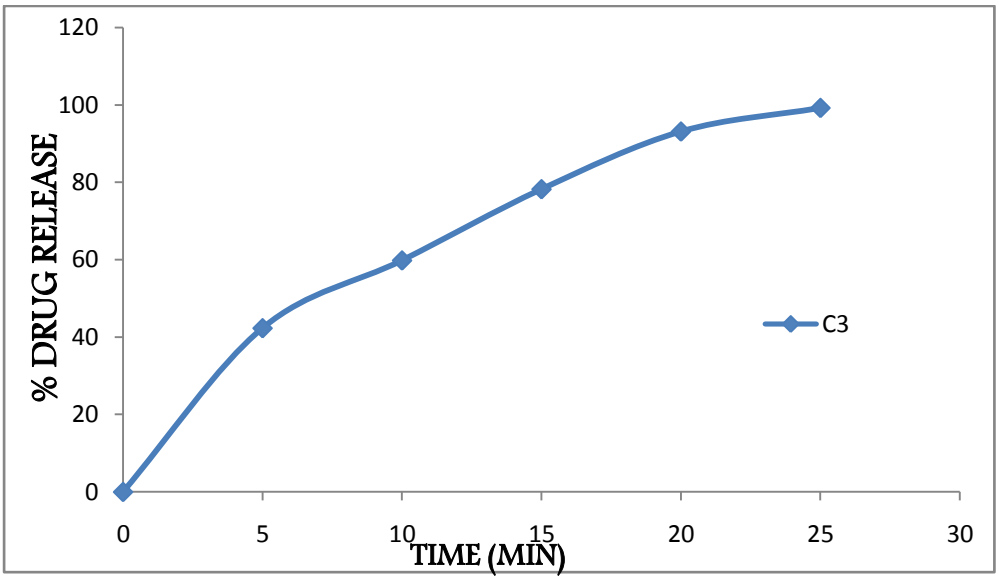
Formulation of [bitter less] mouth dissolving tablet of drug: **Ac-di-sol, sodium starch glycolate and crospovidone granules by sublimation method[8].**

The second approach used in the preparation of fast dissolving tablet of Prochlorperazine Maleate-Ac-di-sol, sodium starch glycolate and crospovidone granules was sublimation method. In this study mouth-dissolving tablet was prepared by using camphor in different ratios, as it sublimes readily. Camphor, which was used as a subliming agent, is non-toxic. Three formulations of drug Ac-di-sol, sodium starch glycolate and crospovidone granules containing camphor in different proportions were prepared by using Mannitol as a diluent**.** It was compressed on single punch tablet machine using 8 mm punches to get tablet of 130 mg weight.

Evaluation of tablet[5, 9]

Tablets prepared by sublimation method were evaluated for hardness, weight variation, wetting time, disintegration time, friability, content uniformity and in-vitro dissolution test**.** Dissolution profile of optimized batch are given in figure no. 2

Figure No. 2: Dissolution of batch C3 (sublimation method).



Comparison of tablets prepared by disintegrant addition and sublimation method

The tablets prepared by both method i.e. disintegrant addition and sublimation method were compared using different parameters like *in-vitro* disintegration time, wetting time, friability and % drug release.

Results and Discussion

Eudragit E 100 was selected for the taste masking of Prochlorperazine Maleate. The taste-masked granules of drug and Ac-di-sol, sodium starch glycolate and crospovidone were prepared by simple mass extrusion technique using syringe. The drug content was found to be 88% in the granules.The physical properties like bulk density, angle of repose and the shape of complex was found to be 0.7843 g/cm3, 27.54 0 and irregular respectively, Hausner's ratio was found to be 1.02. Data indicate granules have good flow-ability. Nine formulations of drug Ac-di-sol, sodium starch glycolate and crospovidone granules (B1-B9) were prepared by varying the concentration of superdisintegrants.

Tablets were prepared using direct compression they all possess uniform weight due to uniform die fill, with acceptable weight variation as per pharmacopoeial specification. The drug content was found to be in the range of 98.95-101.21% (an acceptable limit) and the hardness of the tablet was found to be between 3.13-4.06kg/cm^2. The tablet thickness was found to be 2.19-2.24 mm, friability of tablet was below 1% indicative of good mechanical

resistance. The wetting time of formulated tablets was in the range of 19.66- 46.66 sec and disintegration time of all batches was in the range of 10.33-30.33 sec.

Batch B-9 was selected as optimized batch containing crospovidone as superdisintegrant in 5% concentration. It has less disintegration time of 10.33sec. The dissolution study was carried out and 100.57% of drug release was occurring within 20 min.

The stability study of optimized batch was carried out at 40^{o}C-75% RH. The tablets were found to be stable at such condition and other parameters were found to be unaffected.

On the other hand tablets formulation prepared with camphor (10%, 20%, 30%), the formulation C3 was chosen. This formulation disintegrated faster, 1.31 min., compared to C1 and C2 which showed disintegration time of 2.35 min. and 1.68 min. Hardness of all formulation was found in the range of 3.1 - 4.4 kg/cm^2. All formulation passed the weight variation test. The wetting time of all formulation was in the range of 2-3.15 min. The percent drug release was 100.15% in 25 minutes. The friability problem occurs with the formulation prepared by sublimation method, tablets were more friable, and the friability of batch C3 was found to be 0.96%.

B9 & C3 formulation showed permissible bioavailability, while formulation B9 was found to be best as this formulation showed less disintegration time, good hardness, short wetting time and drug content uniformity. Comparison of tablets prepared by adding superdisintegrants and sublimation method revealed that super-disintegrant addition method was superior to sublimation method. It was concluded that fast dissolving tablet of Prochlorperazine Maleate can be successfully prepared by using both super disintegrants and sublimation method.

Conflict of Interest: We declared that this review does not have any conflict of interest.

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