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Optimization of cross linked tragacanth and comparison of drug release rate profile with synthetic superdisintegrants on metoclopramide orodispersible tablets

P. Divya*, Snehalatha, D. R. Bharathi and N. Raghavendra Naveen
Department of Pharmaceutics, SJM College of Pharmacy, Chitradurga, (Karnataka) - India

Abstract

Fast dissolving dosage forms can be disintegrated, dissolved, or suspended by saliva in the mouth. This fast dissolving tablet disintegrates instantaneously when placed on tongue and releases the drug dissolves or disperses in the saliva. Fast dissolving tablets are useful in patients, like pediatric, geriatric, bedridden, or mentally disabled, who may face difficulty in swallowing conventional tablets or capsules leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style. Present investigation is to optimize the cross linked tragacanth as natural super disintegrants and comparison of drug release profile with SSG, Crospovidone by direct compression using metoclopromide hydrochloride. From the dissolution profiles, Optimized formulation found to be C_3, 1:0.8 in ratio of Dry tragacanth powder and epichlorhydrin. Different drug formulations are prepared by direct compression. From the drug release profiles it is concluded that formulation with 4% of optimized CLT by direct compression have highest drug release of 95.39% at the end of 15mins when compare to other formulations and natural superdisintegrants have more efficiency than synthetic superdisintegrants.

Key-Words: Metoclopromide Hydrochloride, Cross Linked Trgacanth, SSG, Crospovidone

Introduction

Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Many conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration to obtained rapid and complete systemic drug absorption. Such immediate release products results in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. Tablets are the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. Patients, particularly pediatric and geriatric patients, have difficulty in swallowing these solid dosageforms. These patients are unwilling to take these solid preparations due to a fear of choking. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult.

*** Corresponding Author**
Email: divya0041@gmail.com

Inorder to assist these patients, several mouth dissolving drug delivery systems has been developed. When ODT (Oro dispersible Tablets) put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.[1]

Metoclopramide hydrochloride a derivative of para amino benzoic acid, is a commonly prescribed drug used for the management of gastrointestinal disorders such as gastric stasis, gastroesophageal reflux and for the prevention of cancer chemotherapy- induced emesis. In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as ODTs.[2,3]

The main objective of this research is to optimize the concentration of tragacanth powder and epichlorhydrin in preparation of cross linked tragacanth which is natural superdisintegrant and comparison of drug release profile with synthetic supersisintegrants like SSG, Crosspovidone by direct compression method.

Material and Methods

Metoclopramide Hydrochloride was obtained as a gift sample from Wallace Pharmaceuticals pvt. Ltd. Goa, Sodium starch glycolate was obtained from Micro labs, Bangalore; Crospovidone was obtained from Yarrow chemicals, Mumbai. All other chemicals used in the study were of analytical grade.

Methods

Optimization of cross linked tragacanth[4]

A chemical method was used for the preparation of cross linked tragacanth. Dry tragacanth powder and epichlorhydrin in different ratios like 1:0.2, 1:0.5 and 1:0.8 were allowed to react at temperatures ranging from 37^0c to 105^0c. The reaction time was varied in between 45-100min. The results also revealed that at 37^0c, cross linking of tragacanth was not achieved at all the ratios tried in the present study. As the boiling point epichlorhydrin is 116^0c, the cross linking reaction was carried out in the range of 60^0c to105^0c. The temperature of cross linking reaction exhibited significant effect on the reaction rate. Based on the results of intrinsic properties, optimum conditions for cross linking of tragacanth were found to be

a) 1 : 0.8 ratio of tragacanth : epichlorhydrin.
b) Temperature of reaction of reaction as 105^0c.
c) Time of reaction as 95min.

Where P-Polymer

Method of preparation of mixed blend of drug and excipients

All the materials were passed through sieve no. 60. Required quantity of each ingredient was taken for each specified formulation (Mentioned in the following table) and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc).

Compression of tablets by using direct compression technique

Finally magnesium stearate and talc were added to the prepared blend. The mixed blend of drug and excipients was compressed into tablets weighing 200 mg using flat faced punches of 8 mm diameter in a rotary tablet press (Rimek mini press- 1, Model RSB-4, Karnavati Engineering, Ahmedabad). A minimum of 50 tablets were prepared for each batch.

Evaluation of powder blend [5]

Angle of repose

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (q) was calculated using the formula.

$$\Theta = \tan^{-1} (h/r)$$

Bulk density

Apparent bulk density (p_b) were determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula.

$$p_b = M/ V_b$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend were measured. The tapped density (ρ_t) was calculated using formula.

$$\rho_t = M/ V_t$$

Compressibility index

The simplest way for measuring of free flow of powder was compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) was calculated as follows.

$$I = V0 - V_t /V_0 100$$

Where, V_0 is the bulk volume and V_t is tapped volume.

Hausner's ratio

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by the following method

$$\text{Hausner ratio} = \rho_t /\rho_d$$

Where, ρ_t tapped density and ρ_d bulk density lower hausner ratio.

Evaluation of tablets [5,6]

Characterization of Tablets for Physiochemical Parameters

The prepared Metoclopramide HCl Mouth Dissolving Tablets were evaluated for their physicochemical parameters like appearance, weight variation, hardness, friability, thickness and drug content.

Wetting Time and Water Absorption Ratio:

A piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing 6 ml of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. The same procedure without amaranth was followed for determining the water absorption ratio. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation,

$$\mathbf{R = 100 (W a - W b)/W b}$$

Where, W**b** and W**a** were the weights of the tablet before and after study.

***In Vitro* Dispersion Time:**

In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and *in-vitro* dispersion time was performed.

***In-Vitro* Disintegration Study**

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37+1ºC as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37+1ºC. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

In-Vitro Dissolution Studies:[7]

The In-vitro dissolution studies were carried out using USP apparatus type II (paddle) at 50 rpm. The dissolution medium used was pH 6.8 buffer (900 ml) maintained at 37 ± 0.5°C. Aliquots of dissolution media were withdrawn at different intervals and content of Metoclopramide Hydrochloride was measured by determining absorbance at 273.20 nm.

Results and Discussion

Powder mixture of all the formulations were evaluated for various precompression parameters like bulk density, tapped density, Carr's index and Hausner's ratio using tap density apparatus. Bulk density was found in the range of 0.37-0.42 g/cm^3 and tapped density between 0.45-0.48 g/cm^3 as shown in the following table. Compressibility index was found to lie in the range of 8.31-17.50% with fair to good flow properties. Hausner's ratio values are found in the range of 1.09-1.21. Flow properties of powder can be judged from the angle of repose. The angle of repose <30º indicates free flowing material and >40º with poor flow properties. The angle of repose were found in the range of 23.18º-28.32º as given in following table showing that the blend was free flowing and can be used for direct compression.

The formulated tablets are evaluated for the physiochemical properties. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. Hardness was shown in the range of 2.4 to 3.5 Kg/cm^2 in all the formulations. The friability of all formulations was determined. The friability values of none of the formulations exceeded 1%. The results of friability indicate that the tablets were mechanically stable and can withstand rigors of transportation and handling. Thickness of all tablets was between 2.38 to 2.75 mm showing fairly uniform tabletting.

The results of disintegration of all the tablets were found to be within prescribed limits and satisfied the criteria of Orodispersible tablet. The values were found to be in the range of 18 to 39 sec. Wetting time was used as parameter to correlate with disintegration time. The cumulative drug release values after 15 minutes of dissolution were shown in the graphs. The graphical representation of the in-vitro disintegration time and wetting time, % cumulative drug release were shown in the figures.

Conclusion

From the dissolution profiles, Optimized formulation found to be C_3, i.e, 1:0.8 in ratio of Dry tragacanth powder and epichlorhydrin. Different drug formulations are prepared by direct compression. From the drug release profiles it was concluded that formulation with 4% of optimized CLT by direct compression method have shows highest drug release of 95.39% at the end of 15mins when compare to other formulations and natural superdisintegrants after cross linked showed by have more efficiency than synthetic superdisintegrant.

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Table: 1: Composition of Orodispersible Tablets of Metoclopramide Hydrochloride

Ingredients	OC_1	OC_2	OC_3	DS_4	DS_5	DC_6	DC_7	DCT_8	DCT_9
CLT	4	4	4	-	-	-	-	6	8
SSG	-	-	-	6	8	-	-	-	-
Crosspovidone	-	-	-	-	-	6	10	-	-
Lactose	138	138	138	136	134	136	132	136	134
Total weight	200	200	200	200	200	200	200	200	200

Each formulation contains 10mg of Metoclopromide, 40mg of MCC, 2mg of aspartame, 4mg of aerosil, 2mg of Mg.stearate

Table 2: Data of preformulation studies

Formulation	Angle of repose (θ)*	Bulk density (g/cm^3)*	Tapped density(g/cm^3)*	Carr`s index (%)	Hausner's ratio.*
OC_1	25.82 ±0.249	0.3738±0.019	0.4531± 0.017	17.50± 1.72	1.2121±0.082
OC_2	27.16 ±0.315	0.4102±0.016	0.4539 ±0.024	9.62± 1.81	1.1066±0.025
OC_3	26.64± 0.298	0.3827±0.034	0.4509± 0.039	15.12± 1.63	1.1782±0.038
DS_4	28.32± 0.341	0.4033±0.014	0.4763± 0.017	15.32± 1.67	1.1810±0.026
DS_5	27.46± 0.173	0.4152±0.045	0.4792± 0.026	13.35± 1.53	1.1541±0.023
DC_6	23.29± 0.198	0.4072±0.009	0.4837± 0.032	15.81± 1.72	1.1878±0.033
DC_7	25.45 ±0.241	0.3947±0.049	0.4681± 0.022	15.68± 1.27	1.1859±0.062
DCT_8	27.72 ±0.372	0.4276±0.089	0.4664 ±0.037	8.31± 1.37	1.0907±0.045
DCT_9	23.18± 0.127	0.4104±0.019	0.4532± 0.042	9.44± 1.83	1.1042±0.038

* mean ± S.D., n=3 (all the values are the average of three determinations)

Table 3: Results for the physical properties of tablets

Formulation	Hardness (kg/cm^2)	Uniformity of Thickness(mm)	Friability (%)	Uniformity of weight (mg)
OC_1	2.8 ± 0.52	2.45 ± 0.04	0.61	200.68 ± 0.48
OC_2	2.4 ± 0.5	2.38 ± 0.05	0.64	200.26 ± 0.45
OC_3	2.5 ± 0.52	2.72 ± 0.05	0.57	201.09 ± 0.45
DS_4	3.2 ± 0.46	2.47 ± 0.03	0.52	200.94 ± 0.36
DS_5	3.0 ± 0.48	2.53 ± 0.04	0.56	200.64 ± 0.42
DC_6	3.5 ± 0.54	2.48 ± 0.06	0.52	202.13 ± 0.44
DC_7	3.0 ± 0.45	2.55 ± 0.05	0.62	201.29 ± 0.48
DCT_8	2.7 ± 0.55	2.42 ± 0.03	0.54	200.58 ± 0.42
DCT_9	2.5 ± 0.55	2.75 ± 0.05	0.58	201.02 ± 0.45

Table 4: Results for the evaluation of tablets

Formulation	Drug content (%)	Wetting time (sec)	*In-vitro* disintegration time (sec)	% cumulative drug release
OC_1	99.02 ± 0.4	51	31	86.78 ± 0.7
OC_2	99.36 ± 0.2	44	27	88.04 ± 0.2
OC_3	99.82 ± 0.4	40	24	91.13 ± 1.2
DS_4	97.64 ± 0.3	56	39	77.65 ± 0.5
DS_5	98.91 ± 0.2	50	30	80.09 ± 0.8
DC_6	98.86 ± 0.4	52	34	82.47 ± 0.6
DC_7	99.18 ± 0.4	46	27	87.21 ± 1.2
DCT_8	99.69 ± 0.4	35	22	93.68 ± 0.4
DCT_9	98.91 ± 0.2	26	18	98.24 ± 1.4

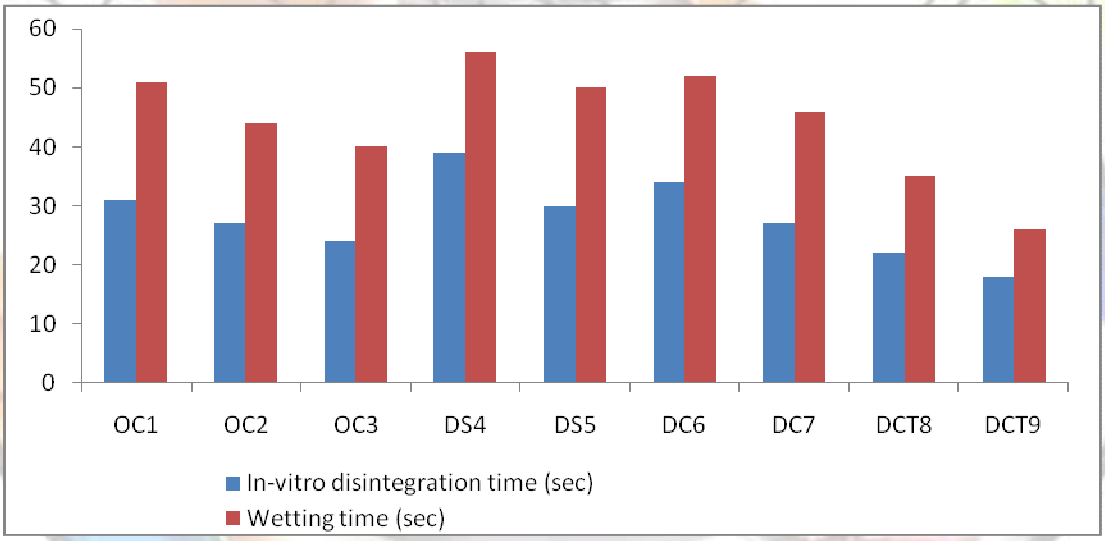

Fig. 1: graphical representation of *in-vitro* disintegration time and wetting time

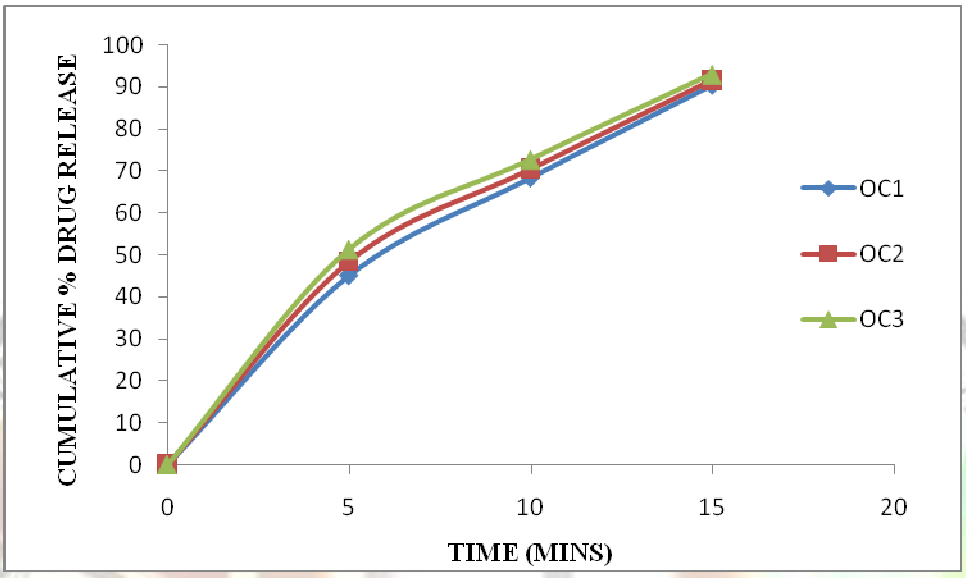

Fig. 2: cumulative % drug release for the batches OC1-OC3

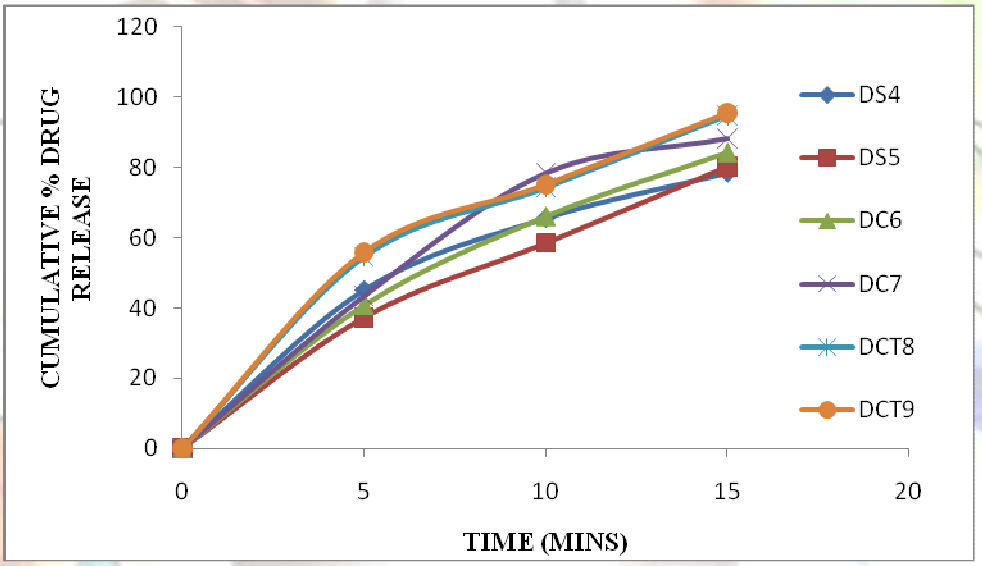

Fig. 3: cumulative % drug release for the formulations