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RESEARCH ARTICLE

Formulation Development of Tramadol Hydrochloride Rapid-disintegrating Tablets Using Simplex Lattice Design

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ABSTRACT

The effect of a mixture of super disintegrants on the disintegration time and in vitro drug release rate was studied. In this study, an attempt had been made to prepare rapid disintegrating tablets of the drug using different super disintegrants following wet granulation method. The sodium starch glycolate, cross carmellose sodium and pregelatinized starch (Starch 1500®) were used in different concentration according to the simplex lattice design as the super disintegrants. The tablets were evaluated for diameter, thickness, hardness, friability, weight variation, wetting time, percentage of water absorption, disintegration time and in vitro dissolution studies. The disintegration time of all formulation showed less than 75 seconds. The formulation F4 showed low disintegration time that is 14 seconds and the percentage drug release was 97.33 within 10 minutes. The tablets containing equal quantity of Starch 1500® and cross carmellose sodium showed lowest disintegration time than other formulation containing Starch 1500®, cross carmellose sodium and sodium starch glycolate in various proportions shown in Table-1.

KEYWORDS: Tramadol hydrochloride, Simplex lattice design, Super disintegrants, Spray drying.

INTRODUCTION:

A large number of patients may have difficulty in swallowing the conventional dosage forms (i.e. tablets and capsules), particularly pediatric and geriatric. Such problems can be overcome by means of developing rapid disintegrating/dissolving tablets. Rapid disintegrating tablets are perfect for these patients as such tablets immediately release the active drug when placed on tounge. The rapid-disintegrating tablets are prepared by techniques such as tablet molding, spray drying, sublimation[1], lyophilization[2], solid deposition[3] or addition of disintegrants[4]. The main criterion for mouth disintegrating tablets is to disintegrate or dissolve rapidly in oral cavity with saliva within a minute without need of water. As tablets disintegrant in mouth, this could enhance the bioavailability of drug through pregastric absorption from the mouth, pharynx and esophagus[5]. The various super disintegrants like sodium starch glycolate[6], cross carmellose sodium[7] and pregelatinized starch[8] were used for preparation of rapid disintegrating tablets. Tramadol hydrochloride, is a non-steroidal anti-inflammatory, slightly water soluble drug was selected as a model drug because it is widely used in treatment of pain and inflammation. To prevent mild after bitter taste of tramadol hydrochloride, sweetening agent, sodium saccharin was used.

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A general problem in formulation development occurs when the components of formulation are varied in an attempt to optimize its performance with respect to variables. Simplex lattice can be used to determine the relative proportion of ingredients that optimizes a formulation with respect to specified variables. For this reason simplex lattice design is used to obtain the optimum concentration of super disintegrants to formulate the rapid disintegrating tablets of tramadol hydrochloride.

MATERIALS AND METHODS:

Materials:

Tramadol hydrochloride was a gift sample from Rantus Pharma Pvt Ltd., Hyderabad (India), Sodium Starch Glycolate (SSG), Cross carmellose sodium (CCS) and Starch 1500® were gift from Merit Organic Chemicals, Sarigam (India), Maruti Chemicals, Ahmedabad (India) and Colorcon Asia Pvt Ltd, Goa (India) respectively. All other ingredients used were of pharmaceutical grade.

Methods:

Spray drying of Mannitol:

Spray drying of mannitol reduced the particle size so that it is rapidly dissolves, which is necessary for the rapid-disintegrating/dissolving type of formulation. Mannitol was spray dried by LabUltima (LU 222) spray dryer. First mannitol was dissolved in water and then sprayed into the drying chamber at feeding rate 2 ml/min with inlet and outlet temperature of 120 ºC and 90 ºC respectively at aspiratration speed of 40. Then the dried mannitol was collected from the cyclone separator.

Table No.1: Formulation of tablets

Batch / Content	F1	F2	F3	F4	F5	F6	F7
TH	100	100	100	100	100	100	100
SSG	25	12.5	-	-	-	12.5	8.33
CCS	-	12.5	25	12.5	-	-	8.33
Starch 1500	-	-	-	12.5	25	12.5	8.33
MS	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mannitol	106.25	106.25	106.25	106.25	106.25	106.25	106.25
Lactose	15	15	15	15	15	15	15
SS	1.25	1.25	1.25	1.25	1.25	1.25	1.25

TH – Tramadol hydrochloride, SSG - Sodium starch glycolate, CCS – Cross carmellose sodium, MS – Magnesium stearate, SS – Sodium saccharin, F – Formulation

Table No. 2: Evaluation of tablets

Batch / Properties	F1	F2	F3	F4	F5	F6	F7
Thickness (mm)	3.42 ± 0.03	3.41 ± 0.01	3.44 ± 0.05	3.42 ± 0.05	3.43 ± 0.02	3.42 ± 0.03	3.44 ± 0.02
Diameter (mm)	8.02 ± 0.04	8.01 ± 0.04	8.02 ± 0.03	8.01 ± 0.05	8.00 ± 0.07	7.98 ± 0.04	8.01 ± 0.06
Hardness (kg/cm^2)	2.7 ± 0.01	3.1 ± 0.03	2.9 ± 0.02	2.6 ± 0.04	2.9 ± 0.01	3.2 ± 0.02	3.3 ± 0.02
Friability (%)	0.69 ± 0.01	0.60 ± 0.01	0.65 ± 0.02	0.71 ± 0.009	0.64 ± 0.01	0.58 ± 0.02	0.44 ± 0.01
Weight variation (%)	1.82 ± 0.02	2.32 ± 003	1.85 ± 0.02	2.09 ± 0.04	3.14 ± 0.02	2.9 ± 0.01	3.03 ± 0.05
Wetting time (sec)	143 ± 0.25	80 ± 0.78	128 ± 0.64	29 ± 0.14	44 ± 0.87	108 ± 0.95	85 ± 0.23
% Water absorption	90.38 ± 1.03	58.33 ± 0.87	77.48 ± 0.34	98.17 ± 1.12	72.25 ± 0.74	73.72 ± 0.58	84.41 ± 0.82
Disintegration time (sec)	75 ± 0.54	44 ± 0.78	72 ± 1.04	14 ± 0.07	21 ± 0.89	63 ± 0.48	29 ± 0.14
% Drug Release	82.19 ± 1.26	89.23 ± 0.83	85.54 ± 1.42	97.33 ± 0.98	91.37 ± 0.64	86.49 ± 0.71	82.7 ± 0.67

Results are the mean of triplicate observations ± Standard Deviation

Preparation of Tramadol hydrochloride Tablets:

Tablets of tramadol hydrochloride were made by wet granulation method using ingredients given in Table-1. The various batches were prepared using mixture of three super disintegrants namely Starch 1500®, cross carmellose sodium and sodium starch glycolate according to simplex lattice design. Disintegrants were mixed with spray-dried mannitol. Then the powder blend was mixed with drug and adds purified water to obtain a coherent mass. The wet mass was passed through a 30 mesh. The wet granules were dried at 60 ºC for 1 hour in hot air oven. The dried granules were mixed with magnesium stearate. The final weight of tablets was kept 250 mg. This blend was compressed into tablets using 8 mm diameter die using Technosearch KBr press. The hardness of the tablets was kept between 2.5 and 3 kg/cm^2. The prepared tablets were stored in airtight container and were evaluated for various parameters.

Evaluation of Tablets:

Formulated tablets were evaluated for diameter, thickness, hardness, friability, and weight variation, wetting time, percentage of water absorption, disintegration time and in vitro dissolution studies. The diameter and thickness was measured using Mitutoyo Digimatic Caliper. Hardness was measured using Monsanto hardness tester. Friability was determined by Roche friabilator by evaluating 20 tablets.

Wetting time was determined by placing a piece of tissue paper folded twice in a small petridish containing 6 ml water. A tablet was placed on the tissue paper and small amount of amaranth powder was placed on upper surface of tablet. The time required to develop the red color on the upper surface of the tablet was recorded as wetting time of tablet[4].

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was kept on paper and time required for complete wetting was measured. Then wetted tablet was weighed and percentage of water absorption was determined using the following equation[9]:

$R = Wb\text{-}Wa/Wa \times 100$

Where, Wa = Weight of tablet before water absorption

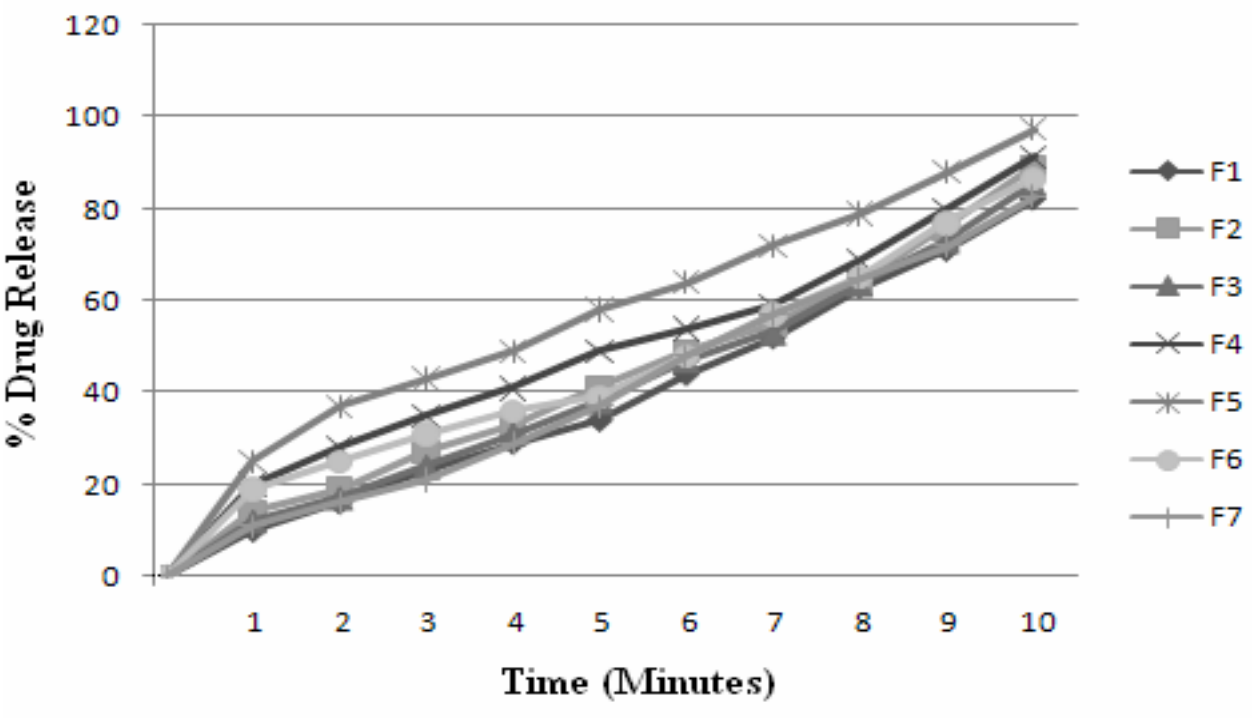
Wb = Weight of tablet after water absorption

In vitro disintegration time was determined by Lab Hosp disintegration test apparatus. This test was carried out at 37 ± 2 ºC in 900 ml of distilled water. In-vitro dissolution studies were carried out using USP apparatus type II at 50 rpm. The dissolution medium used was phosphate buffer pH 6.4 (900 ml) maintained at 37 ± 0.5 ºC. 5 ml of sample was withdrawn and replaced with fresh dissolution medium at different time intervals and concentration of tramadol hydrochloride was measured by determining absorbance at 272 nm using Jasco V-530 UV spectrophotometer.

RESULT:

The average weight of the prepared tablets was found between 252.18 and 256.07. The average thickness and diameter of tablets were found to be 3.425 mm and 8.0071 mm respectively. The hardness of prepared tablets was found between 2.5 to 3.5 kg/cm^2. The friability of all the formulations was found to be less than 1%. The percentage of water absorption was measured and found between 58.33 and 98.17. The disintegration time of the tablets varied from 14 to 75 seconds. The drug release profile of all formulations is shown in Figure-1.

Figure No. 1: Drug Release Profile



DISCUSSION:

The results show resistance to loss of weight, which indicates the capability of tablet to withstand abrasion in handling packaging and shipment. The weight variation of prepared tablets was within the limits. The wetting time of formulation F4 was 29 seconds which contains Starch 1500® and cross carmellose sodium in equal proportion, which was lower than other formulations. The in-vitro drug release of tablets prepared by Starch 1500® and cross carmellose sodium was found 97.33 % and drug release of tablets containing only sodium starch glycolate was 82.19 % while tablets formulated with sodium starch glycolate and starch 1500 showed release 86.49 % within 10 minutes.

The outcome of simplex lattice design revealed that the combination of disintegrants significantly affect the wetting time, percentage water absorption, disintegration time and drug release. The formulation containing Starch 1500® and cross carmellose sodium in equal proportion showed the rapid disintegration of tablets then the other formulation as shown in Table-2. This rapid disintegration of such types of tablets was due to the penetration of water into the pores of the tablets, which lead to the swelling and wicking of super disintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablet. It is, therefore, concluded that by selecting appropriate amount and blend of disintegrants in tablets formulation, tablet with rapid disintegration can be produced with least efforts.

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