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RESEARCH ARTICLE

Formulation Development and Evaluation of Fast Dissolving Tablets of Tramadol Hydrochloride

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ABSTRACT

Mouth dissolving tablets / fast dissolving tablets is gaining prominence as new drug delivery systems. These dosage forms dissolve or disintegrate in oral cavity within a matter of seconds without need of water or chewing. The present investigation of research is oriented through increasing safety and efficacy of existing drug molecule through novel concept of drug delivery. Tramadol hydrochloride is a centrally acting analgesic, which is orally and intravenously administered drug. Fast dissolving tablets of Tramadol hydrochloride were prepared by using superdisintegrants such as crospovidone, croscarmellose sodium and sodium starch glycolate in combinations and at different concentrations. The prepared batches were evaluated for organoleptic properties, hardness, friability, weight variation, *in vitro* dispersion time, wetting time, *in vitro* drug release studies and stability studies. The drug-excipients interaction was checked and found negative through Infrared spectroscopy and Differential scanning calorimetry studies. Formulation prepared by using superdisintegrants containing crospovidone 10% w/w and croscarmellose sodium 10% w/w respectively, showed minimum time for disintegrate, dispersion and drug release almost 100 % in 10 minutes. Finally it was concluded that FDTs of Tramadol hydrochloride can be successfully formulated with improved patient compliance.

KEYWORDS

Tramadol Hydrochloride, Superdisintegrants Croscarmellose Sodium, Crospovidone, Sodium Starch Glycolate

INTRODUCTION

Pediatric and geriatric patients may have difficulties in swallowing or chewing pharmaceutical dosage forms for oral administration. Tablets that rapidly dissolve upon contact with saliva in the buccal cavity could present a solution to those problems and so there is an increased interest in fast dissolving dosage forms for buccal, sublingual and oral administration.

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Fast dissolving tablets (FDTs) are perfect fit for these patients as these tablets immediately release the active drug when placed on tongue by rapid disintegration / dispersion, followed by dissolution of drug.[1-3] Mouth dissolving tablets (MDTs) can be prepared by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying and sublimation. MDTs disintegrate and / or dissolve rapidly in the saliva without the aid of water, releasing the drug. Some drugs are absorbed from the mouth, pharynx and esophagus 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.[4,5]

Tramadol hydrochloride is a centrally acting analgesic structurally related to codeine and morphine used in the treatment of moderate to severe pain in diverse conditions. Routes other than oral, like intravenous, which are used to administer tramadol, in acute conditions like postoperative neuralgia or situations when the patient is hospitalized. Unlike insulin, tramadol must be injected under the supervision of a physician only. Patients suffering from arthritis or neuralgia have to take the therapy for longer duration of time. In such cases, oral route is the preferred route. Thus, the problems like bitter taste and ease of swallowing need to be solved for tramadol therapy. The objective of this work was to formulate and optimize MDTs of Tramadol hydrochloride that disintegrate in a few seconds and still have good mechanical strength.

Now a day, the natural polymers are also playing a vital role in the drug delivery systems which are showing less side effects, cost effective with wide spread availability in all the natural regions around the world. Hence to formulate a MDTs, crospovidone and treated agar are used as superdisintegrant in the preparation of mouth dissolving tablets and which can be taken without water to offer high patient compliance, easy to formulate, suitable to market and possess industrial applicability.

MATERIALS AND METHOD

Tramadol HCl was a gift sample obtained from Cadila Pharmaceuticals Ltd, Ahmedabad, Gujarat, India, was taken as model drug. Microcrystalline cellulose (Avicel PH 102) was supplied by Ozone international, Mumbai. Crospovidone was obtained from the Aurobindo pharma, Hyderabad. Sodium Starch Glycolate was a gift sample obtained from Arihant Trading Co., Mumbai. Croscarmellose sodium was supplied by Signet Corporation, Mumbai. Magnesium stearate obtained from Cipla Ltd, Mumbai. All the ingredients received were of pharmaceutical grade. Other materials and solvents used were of analytical grade.

Pre-Formulation Study

Standardization of the drug was carried out using phosphate buffer pH 6.8 by UV spectrophotometer (UV-160A, SHIMADZU). Solubility analysis of drug in various solvents including water, phosphate buffer pH 6.8, and organic solvents like ethanol, methanol, chloroform and acetone was carried out.

Preparation of Mouth Dissolving Tablets

Ten formulations were prepared by wet granulation method using superdisintegrants such as sodium starch glycolate, croscarmellose and crospovidone in various ratios as given in Table 1.

By Adding Super-disintegrating Agent

All the ingredients were passed through sieve #60 and kept in a hot air oven at 60°C to make anhydrous and accurately weighed. The drug, mannitol, starch were passed through sieve #60 and mixed by geometric dilution method to improve the drug distribution and content uniformity. Wet granulation method was carried out. Pass the mass through sieve #20 and dry in fluidized bed dryer. Pass the granules through sieve #30 to obtain granules of uniform size and collect in suitable container. The magnesium stearate, talc, aspartame, MCC-pH 102, superdisintegrants, flavour were passed through sieve #80, mixed and blended well with the initial mixture. The mixed blend of drug and the excipients was compressed using REMEK 10 station rotary punching machine to produce tablet weighing 200 mg having a diameter of 8 mm. Following the procedure, ten batches of FDTs of Tramadol hydrochloride in different ratios of superdisintegrants were prepared.[6]

Evaluation of Lubricated Granules

The lubricated granules prepared were evaluated for the following parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose as per official procedures.

Evaluation of Tablets

All the compressed tablets were evaluated for the following parameters.[7-10]

General Appearance

Tablets of different formulations were randomly selected and organoleptic properties such as color, odor, taste and shape, were evaluated.

Thickness

Thickness of tablets was determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

The hardness was determined by using the Monsanto hardness tester.

Friability

The friability was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of Weight

Twenty tablets were randomly selected from each formulation, individually weighed and the average weight was calculated.

In vitro Dispersion Test

This test was performed to ensure disintegration of tablets in the salivary fluid, as it is used for mouth dissolving tablet. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 5ml of simulated salivary fluid of pH 6.8. Five tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

Drug Content

Five tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of average tablet was taken from the crushed blend. The samples were transferred to 100 ml volumetric flasks and were diluted with phosphate buffer pH 6.8. The content was shaken periodically and kept for one hour to dissolve of drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ_{max} 271 nm against blank reference.

Wetting Time and Water Absorption Ratio

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 6 ml of simulated saliva pH 6.8. A tablet having amaranth powder on the upper surface was placed on the filter paper. Time required to develop red color on the upper surface of tablet was recorded as wetting time. Three tablets from each formulation were randomly selected and the average wetting time was noted. Wetting time corresponds to the time taken for the tablet to disintegrate when placed gently on the tissue paper in a petridish. This method will duplicate the *in vivo* disintegration as the tablet is motionless on the tongue. Less wetting time indicates more porous the tablets. The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation.[11]

$$R = 100 \times [W_a - W_b] / W_b$$

Where, Wb = weight of the tablet before water absorption, Wa = weight of the tablet after water absorption.

In vitro Dissolution Studies

In vitro drug release studies were carried out by using USP Dissolution Apparatus II (Paddle Type) at 50 rpm. The drug release profile was studied in 900 ml of phosphate buffer solution, pH 6.8 maintained at 37 ± 0.5°C. Aliquots of 5 ml of dissolution medium were withdrawn at specific time intervals (1, 3, 5, 10, 15, 20, 25, and 30 minutes), the fresh dissolution medium was replaced every time with the same quantity of the sample. The collected samples were analyzed at 271 nm using phosphate buffer solution pH 6.8 as blank. The cumulative percentage drug release was calculated.[12]

RESULTS AND DISCUSSION

Evaluation of Powder Blend

Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external

Table 1: Compositions for FDT of Tramadol hydrochloride

Ingredients	**A (mg)**	**B (mg)**	**C (mg)**	**D (mg)**	**E (mg)**	**F (mg)**	**G (mg)**	**H (mg)**	**I (mg)**	**J (mg)**
Tramadol HCl	50	50	50	50	50	50	50	50	50	50
Croscarmellose Sodium	10	10		10	6	-	10	10	4	4
Sodium starch glycolate	4		10	10	10	1	-	-	-	-
Crospovidone	-	-	-	-		10	10	4	10	4
Aspartame	7	7	7	7	7	7	7	7	7	7
Microcrystalline cellulose	80	80	80	80	80	80	80	80	80	80
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4
Flavours	2	2	2	2	2	2	2	2	2	2
Mannitol	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Starch	10	10	10	10	10	10	10	10	10	10
Total	200	200	200	200	200	200	200	200	200	200

Table 2: Evaluation of powder blend

Batch	**Loose bulk density (gm/cc)**	**Tapped bulk density (gm/cc)**	**Angle of repose θ (º)**	**Compressibility index (%)**	**Hausner's ratio**
A	**0.500**	0.588	28.49	15.00	1.19
B	**0.513**	0.609	28.95	15.79	1.15
C	**0.517**	0.595	28.23	13.16	1.19
D	**0.512**	0.612	27.60	16.22	1.18
E	0.518	0.601	29.21	13.80	1.10
F	0.497	0.584	28.33	15.00	1.18
G	0.510	0.599	26.91	15.00	1.18
H	0.544	0.628	28.85	13.33	1.15
I	0.543	0.635	27.03	13.04	1.15
J	0.538	0.651	29.51	13.14	1.16

loading as might be applied in mixing and tableting. Values of angle of repose range of 26.91 to 29.51°. Carr's index of the prepared blends falls in the range of 13.04 to 16.22 % and this is also supported by Hausner's ratio values which were in the range of 1.10 to 1.19. The results are given in Table 2. Hence, the prepared blends possessed good flow properties and these can be used for tablet manufacture.

Evaluation of Core Tablets

All the tablets were prepared under similar conditions. All the formulations exhibited white color, odorless, convex in shape with smooth surface. The physical properties of the tablets are shown in Table 3. The average weight of the fast dissolving tablets (FDTs) prepared by wet granulation method was 198.00 to 203.38 mg. Hardness and friability of all formulations was within acceptable limits. Hardness of tablets prepared by direct compression was 2.98 to 3.12 kg/cm^2. The friability of all formulations was found to be less than 1.0 % and hence the tablets with lower friability may not break during handling on machines and or shipping. Average thickness of tablets is 3.84 mm, diameter is 8 mm.

Wetting time is very important for FDTs which is desired to be less than 60 seconds for orally disintegrating tablets. This assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Wetting time of prepared FDTs was in the range of 19.22 to 164.2 seconds as depicted in Table 4 and the order of superdisintegrants was Crospovidone < Ac-Di-Sol < SSG. As the concentration of superdisintegrants in the formulations increased the wetting time was found to decrease. Wetting time was used as an indicator from the ease of the tablet disintegration in buccal cavity. After contact with water the tablets containing SSG swelled, the outer edge appeared gel-like. Tablets containing crospovidone quickly wicks water and were hydrated, but were soft as compared with tablets prepared with Ac-Di-Sol and SSG. The centers of the tablets with SSG and Ac-Di-Sol remained dry and hard. The % drug content of the prepared tablets as shown in Table 4 was in the range of 99.23 to 101.4%. The correlation of variation was found to be less than 0.010%, indicating uniformity of the drug content in the prepared tablets.

All the formulations were prepared using the combination of superdisintegrants crospovidone, croscarmellose and sodium starch glycolate. The drug release for batch A, B, C, D, E, F, G, H, I and J were found to be 94.5 %, 92.5 %, 93.1 %, 95.10%, 93.12%, 98.50 %, 99.14 %, 97.95 %, 98.07 and 97.12 % respectively in 15 minutes. Whereas, the formulation 'G' shows drug release almost 100% in the 15 minutes. The drug release for batches is shown in Table 5 and 6. The *in vitro* dissolution profile of formulation is given in Figure 1 and 2.

The optimum concentration of superdisintegrants used in various combinations results in the rapid swelling of tablet in dissolution medium resulting in rapid dispersion of tablets and release of drug from the formulation prepared by superdisintegrants addition. With reference to the type of superdisintergrant, the release rate was found to follow the order: Crosprovidone > Ac-Di-sol > SSG.[13] From the past experiences, we can say that the faster disintegration of tablets containing crospovidone may be attributed to its rapid capillary activity and pronounced hydration with little tendency to gel formation. Thus, the results suggest that the dispersion time can be decreased by using wicking type of disintegrants.

Stability Studies

The optimized formulation of Tramadol hydrochloride tablets was selected for the stability studies. The accelerated stability studies were carried out according to ICH guidelines by storing the samples at 40 $\pm$ 2^{o}C and 75 $\pm$ 5% RH for 1 month. The tablets were evaluated for hardness, drug content, *in vitro* dispersion time and dissolution study as shown in Table 7 and 8, and compared with tablets which were evaluated immediately after manufacturing.

Table 3: Physical properties of prepared MDT

Batch	Hardness (kg/cm^2)	Friability (%)	Uniformity of weight (mg)	Thickness (mm)	Diameter (mm)
A	3.0	0.097	203.5	3.84	8.015
B	3.05	0.104	199.0	3.82	8.110
C	3.12	0.028	201.5	3.84	8.012
D	2.98	0.164	198.5	3.83	8.100
E	3.20	0.132	203.0	3.67	8.123
F	3.0	0.097	203.5	3.39	8.015
G	3.10	0.049	199.8	3.50	8.043
H	3.20	0.161	200	3.28	8.131
I	2.98	0.164	198.5	3.18	8.056
J	3.19	0.043	199.8	3.27	8.010

Table 4: Evaluation parameters of prepared MDT

Batch	% Drug Content	Wetting time (seconds)	*In vitro* Dispersion Time (seconds)	Water absorption ratio (%)
A	99.96	60.24	46.55	67.31
B	99.23	80.98	69	70.05
C	100.40	130.25	100.33	79.65
D	98.64	164.2	130	63.18
E	100.96	149.2	75	65.76
F	99.96	60.24	46.55	67.31
G	100.74	19.22	15.63	55
H	101.1	20.54	19.69	62.18
I	98.07	30.2	23.05	70.18
J	99.25	55.2	40.24	75.76

Table 5: Data for *in vitro* drug release profile of Tramadol hydrochloride tablets of batches A to E

Time in minute	Cumulative percentage of drug released in %				
	A	B	C	D	E
0	0	0	0	0	0
1	26.04	29.64	25.08	19..22	22.14
3	36.56	42.79	38.90	34.27	34.56
5	58.04	61.38	58.94	59.04	54.67
10	74.21	80.81	77.53	80.04	73.52
15	94.5	92.50	93.10	95.10	93.12

Table 6: Data for *in vitro* drug release of Tramadol hydrochloride tablets of batches F to J

Time in minute	Cumulative percentage of drug released in %				
	F	G	H	I	J
0	0	0	0	0	0
1	36.04	42.72	38.76	42.56	37.24
3	50.56	61.56	50.86	53.27	47.69
5	68.04	73.30	63.88	67.40	58.97
10	73.21	90.41	78.35	80.23	79.52
15	98.50	99.14	97.95	98.07	97.12

Table 7: Data for evaluations for physical appearance after stability studies of FDT of Batch 'G'

Various parameters Formulation G	Observation of tablets for different parameters with respect to time elapsed		
	Zero day	After 15 days	After 1 month
Color	Colorless	Colorless	Colorless
Odour	Odourless	Odourless	Odourless
Hardness(kg/cm^2)	3.1	2.8	2.8
% Drug content	99.71	97.62	98.72
In vitro dispersion time(secs)	16.07	18.55	17.55

Table 8: *In vitro* release of Tramadol hydrochloride from tablets of on zero day, 15 days samples and after one month accelerated stability studies of 'G'.

Time in min	Cumulative percentage of drug released		
	zero day	15 days	one month
1	42.72	40.72	39.72
3	61.56	57.56	60.56
5	73.30	70.30	75.30
10	90.41	90.41	91.41
15	99.14	98.14	99.54

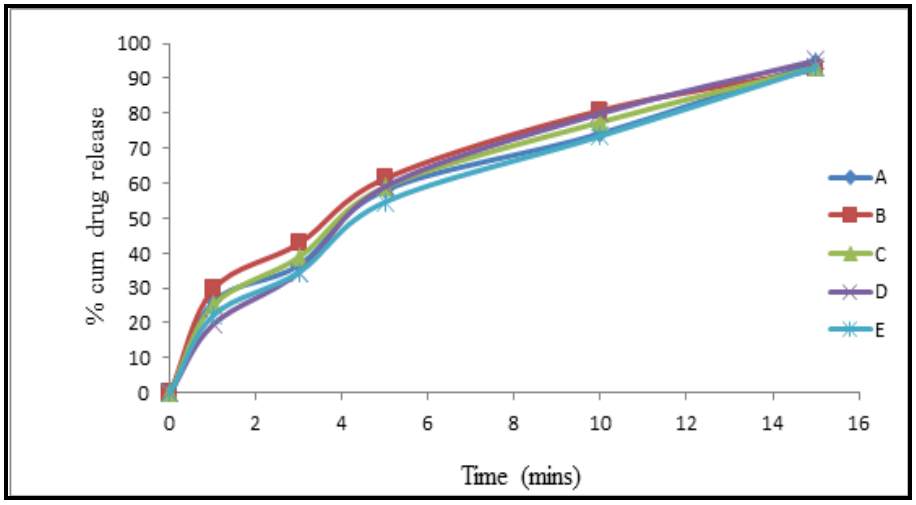

Figure 1: *In-vitro* dissolution profile of formulation batches A-E

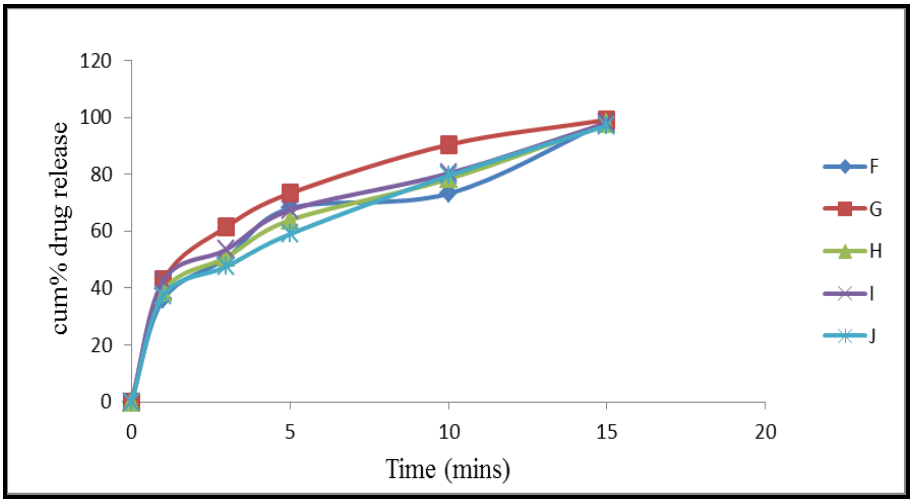

Figure 2: *In-vitro* dissolution profile of formulation batches F-J

CONCLUSION

In the present study it can be concluded from the characterization of fast dissolving tablets of Tramadol hydrochloride that formulation containing crospovidone & croscarmellose sodium was most acceptable. The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability. *In vitro* drug release from the tablets shows significantly improved drug dissolution. Hence, it could be concluded that the superdisintegrant based orodispersible tablets of tramadol hydrochloride would be quite effective in pain, providing quick onset of action without need for water for swallowing or administration. Further *in vivo* studies in human volunteers are required to correlate *in vitro* release data.

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