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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF MOUTH DISSOLVING TABLET OF TRAMADOL HYDROCHLORIDE

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ABSTRACT

Many patient groups, such as the elderly, children, mentally retarded, uncooperative or nauseated, have difficulty in swallowing conventional dosage forms, like tablets. Swallowing conventional tablets will be further hindered by conditions such as unavailability of water, allergic reactions and episodes of coughing[1]. These problems can be solved by developing rapidly disintegrating and dissolving tablet dosage forms for oral administration, because they dissolve in saliva and does not require water for swallowing. Upon ingestion, the saliva serves to rapidly dissolve the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and oesophagus, as the saliva passes down in to the stomach. In these cases, the bioavailability of drugs is significantly greater than those observed from conventional dosage forms[2]. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets[3]. A wide range of drugs requiring quick onset of action are the promising candidates for this dosage form. These include neuroleptics, antidepressants, cardiovascular drugs, analgesics and so on.

Fast dissolving tablets (FDTs) can be prepared by different methods, such as direct compression, freeze-drying, spray drying, sublimation, wet granulation method[4]. The basic approach for the development of FDTs is the use of superdisintegrants.

The aim of this study was to formulate FDTs with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity without water. To achieve this goal, mannitol used as diluent and aspartame as sweetening agent for the formulation of tablets. Attempts were made to enhance dissolution rate along with faster disintegration using superdisintegrants, like croscarmellose sodium, sodium starch glycolate and crospovidone. Tramadol hydrochloride, a centrally acting synthetic opioid analgesic, was selected as the active pharmaceutical ingredient in the study.

Keywords: Tramadol hydrochloride, orodispersible tablet, croscarmellose sodium, crospovidone, superdisintegrant addition method.

INTRODUCTION

Many patient groups, such as the elderly, children, mentally retarded, uncooperative or nauseated, have difficulty in swallowing conventional dosage forms, like tablets. Swallowing conventional tablets will be further hindered by conditions such as unavailability of water, allergic reactions and episodes of coughing[1]. These problems can be solved by developing rapidly disintegrating and dissolving tablet dosage forms for oral administration, because they dissolve in saliva and does not require water for swallowing. Upon ingestion, the saliva serves to rapidly dissolve the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and oesophagus, as the saliva passes down in to the stomach. In these cases, the bioavailability of drugs is significantly greater than those observed from conventional dosage forms[2]. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets[3]. A wide range of drugs requiring quick onset of action are the promising candidates for this dosage form. These include neuroleptics, antidepressants, cardiovascular drugs, analgesics and so on.

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MATERIALS AND METHODS

Materials

Tramadol hydrochloride was obtained as gift sample from Cadila Pharmaceutical Ltd., Ahemdabad. Croscarmellose sodium, crospovidone and sodium starch glycolate were obtained as gift samples from Signet Corporation, Mumbai, Aurobindo Pharma, Hyderabad, Arihant Trading Co., Mumbai, respectively.

Methodology

Identification of drug

The drug was identified using FT-IR.[5]

Solubility study of Tramadol HCl[6]

Solubility of the drug was determined in different media (distilled water, 0.1 N HCl, phosphate buffer pH 6.8, acetate buffer and phophate buffer 7.4). Accurately weighted drug was transferred in volumetric flasks containing different solvents and was shaken until saturation was achieved; the flask was sonicated for 30 min.

Calibration curve of Tramadol hydrochloride in phosphate buffer solution, pH 6.8

Tramadol hydrochloride (20 mg) was dissolved in little quantity of phosphate buffer 6.8 solution and volume was made up to 100 ml

with the same solution. Appropriate aliquots were taken into different volumetric flasks and volume was made up to 10 ml with phosphate buffer 6.8 solution in each, so as to get drug concentrations of 20, 40, 60, 80, 100, 120, 140 and 160 µg/ml. The absorbences of these solutions were estimated at λ_{max} 271 nm.

Wet granulation method for tablet preparation

Each tablet containing 50 mg of Tramadol hydrochloride was prepared by wet granulation technique. The superdisintegrants, sodium starch glycolate-SSG (0.5%, 5% and 2%), croscarmellose sodium-CCS (2%, 3% and 5%) and crospovidone-CP (2% and 5%) were used in different proportions and in different combinations (Table 1). The drug, mannitol, starch were passed through sieve #60 and mixed using geometric dilution method to improve the drug distribution and content uniformity and then triturated well in a mortar. Wet granulation, was carried out with moisture activation. The final mass was passed through sieve #20 and the granules thus obtained, were dried in hot air oven at 60°C for 15-20 min. The granules were then passed through sieve #30 and collected in suitable container. Then magnesium stearate, talc, aspartame, MCC-pH 102, superdisintigrant, flavour were passed through sieve #80, mixed and blended well with the initial mixture. The mixed blend of the 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 orodispersible tablets of Tramadol hydrochloride in different ratios of superdisintegrants were prepared.

Table 1: It shows the various compositions for FDTs of Tramadol hydrochloride by superdisintegrant addition method

Ingredients	A (mg)	B (mg)	C (mg)	D (mg)	E (mg)	F (mg)	G (mg)	H (mg)	I (mg)	J (mg)
Tramadol hydrochloride	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 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg

Evaluation of fast dissolving tablets of Tramadol hydrochloride

Thickness and dimension

Tablets of each batch were selected and measured for thickness and diameter using digital screw gauge (Micrometer, Mitutuyo, Japan).

Hardness of the tablets[7]

The tablet should be stable to mechanical stress during handling and transportation. The hardness was tested using Monsanto hardness tester.

Friability of tablets[7, 8]

Friability of the tablets was determined using Roche friabilator at 25 rpm/min for 4 min. Ten tablets were weighed and loss in weight (%) was calculated.

Weight variation test[7]

Twenty randomly selected tablets were weighed individually and all together. The average weight and the percentage deviation were calculated. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The percentage deviation was calculated using the following formula:

$$\text{Percentage Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

As per Indian Pharmacopoeia (IP), permissible limit of weight variation is 7.5% for tablet weight of 200 mg (Table 2).

Table 2: It shows IP (2007) standards for percentage weight variation[7]

Average Weight of Tablet	± Percentage Deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

Drug content estimation

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. Then, the samples were transferred to 100 ml volumetric flasks and were diluted up to the mark 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.

Wetting time and water absorption ratio[9]

Wetting time of dosage form is related with the contact angle. A lower wetting time implies a quicker disintegration of the tablet.

MethodFive circular tissue papers of 10 cm diameter were placed in a Petri dish with 10 cm diameter. Ten ml of water containing Eosin, a water soluble dye, was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet was noted as wetting time.

Water absorption ratio (R) was calculated using the formula,

$$\mathbf{R = 100 \times [W_a - W_b] / W_b,}$$

Where, W_a = weight of tablet after absorption

W_b = weight of tablet before absorption

***In vitro* dispersion time[10]**

The disintegration time for mouth dissolving tablets needs to be modified, as disintegration is required without water; thus the test should mimic disintegration in salivary content. For this purpose, a Petri dish (10 cm diameter) was filled with 9 ml of phosphate buffer solution, pH 6.8 (which correlated pH of saliva). The tablet was carefully put in the center of Petri dish and time for the tablet to completely disintegrate into fine particles was noted.

***In vitro* drug release studies[11]**

In vitro drug release studies were carried out by using USP XXIII 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 min.) and each time the volume withdrawn was replenished with fresh solvent. The collected samples were analysed at 271 nm using dissolution medium as blank. The cumulative percentage drug release was calculated.

Comparison with marketed product

Following the procedure for *in vitro* drug release studies, drug release profile of marketed product of Tramadol hydrochloride was also determined and compared with the best formulation among the all batches.

Stability studies[12]: The optimized formulation of Tramadol hydrochloride tablets was selected for the stability studies. The accelerated stability studies were carried out according to International conference on harmonisation (ICH) guidelines by storing the samples at 40 ± 2°C and 75 ± 5% RH for 1 month. The tablets were evaluated for hardness, drug content, and dissolution study and compared with tablets which were evaluated immediately after manufacturing.

RESULTS AND DISCUSSION

Identification of drug

FT-IR graph was obtained for identification of various functional groups. Characteristic stretching is shown in Table 3. IR spectrum of Tramadol hydrochloride is shown in Fig.1.

Table 3: It shows FT-IR data of Tramadol hydrochloride

Ingredients	Principal Peaks (cm^{-1})					
Functional Groups	**C-H str (Aromatic)**	**C-H str (Aliphatic)**	**N-H str**	**C-N str**	**C=C str**	**C-O str**
Pure Drug	2929.34	2674.78	3344.93	1289.4	1606.41	1202.9

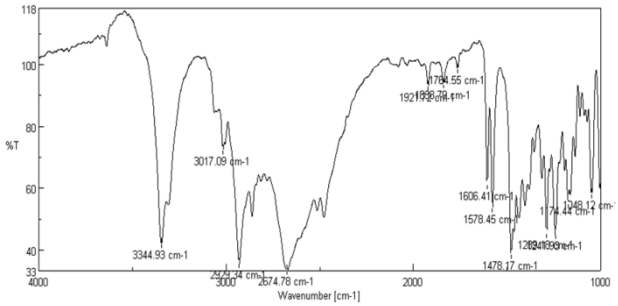

Figure1: It shows IR spectrum of Tramadol hydrochloride

Solubility study of Tramadol HCl

Solubility of the drug was determined in 5 different media, given in Table 4. It was found that drug was freely soluble in water, 0.1 N HCl and 6.8 phosphate buffer.

Table 4: It shows solubility of Tramadol hydrochloride

Media	Solubility (mg/ml)
Water	1.785
0.1N HCl	1.742
6.8 Phosphate buffer	2.014
4.5 Acetate buffer	0.4659
7.4 Phosphate buffer	0.98l2

Calibration curve of Tramadol hydrochloride in phosphate buffer solution, pH 6.8

The absorbance values are listed in Table 5. The data had correlation coefficient of 0.999.The absorbance value showed that it had linear regression and maximum concentration was found to be 160 µg/ml. It followed Lambert Beer's law. The standard plot of Tramadol hydrochloride is shown in Fig.2.

Table 5: It shows calibration curve data for Tramadol hydrochloride

Sr. No.	Concentration (µg/ml)	Absorbance at 271 nm
1	0	0
2	20	0.126
3	40	0.227
4	60	0.359
5	80	0.467
6	100	0.572
7	120	0.689
8	140	0.802
9	160	0.922

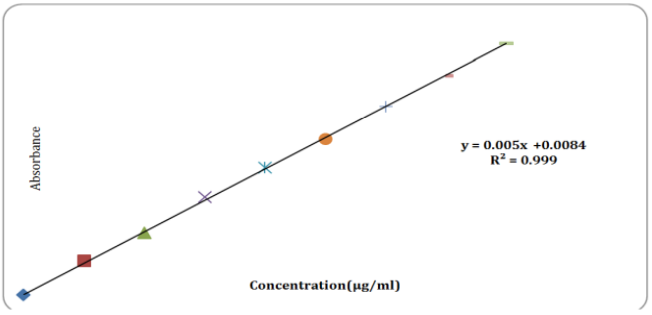

Figure 2: It shows standard plot of Tramadol hydrochloride in phosphate buffer pH 6.8

Evaluation of fast dissolving tablets of Tramadol hydrochloride

Evaluation parameters of prepared FDTs of Tramadol hydrochloride are listed in Table 6.

Table 6: It shows evaluation parameters of prepared FDTs

Batch	Parameters for Batch A-J								
	Thickness (mm)	Diameter (mm)	Hardness (kg/cm²)	Friability (%)	Uniformity Of Weight (mg)	% Drug Content	Wetting Time (sec)	Water Absorption Ratio (%)	*In vitro* Dispersion Time (sec)
A	3.84	8.015	3.00	0.097	203.5	99.96	60.24	67.31	46.55
B	3.82	8.110	3.05	0.104	199.0	99.23	80.98	70.05	69.00
C	3.84	8.012	3.12	0.028	201.5	100.40	130.25	79.65	100.33
D	3.83	8.100	2.98	0.164	198.5	98.64	164.2	63.18	130.00
E	3.67	8.123	3.20	0.132	203.0	100.96	149.2	65.76	75.00
F	3.39	8.015	3.0	0.097	203.5	99.96	60.24	67.31	46.55
G	3.50	8.043	3.10	0.049	199.8	100.74	19.22	55.00	15.63
H	3.28	8.131	3.20	0.161	200	101.1	20.54	62.18	19.69
I	3.18	8.056	2.98	0.164	198.5	98.07	30.20	70.18	23.05
J	3.27	8.010	3.19	0.043	199.8	99.25	55.20	75.76	40.24

In vitro release profile of prepared FDTs is shown in Table 7.
In vitro dissolution studies of various FDT formulations at different time intervals are reported in Fig. 3 & 4.
The drug release for batch A, B, C, D, E, F, G, H, I and J were found to be 94.50%, 92.50%, 93.10%, 95.10%, 93.12%, 98.50%, 99.14%, 97.95%, 98.07% and 97.12%, respectively, in 15 min., whereas, the formulation 'G' showed drug release of almost 100% in 15 min.

Table 7: It shows *in vitro* release profile of cumulative percentage drug release of prepared FDTs

Time in Min.	Cumulative % Drug Release									
	A	B	C	D	E	F	G	H	I	J
0	0	0	0	0	0	0	0		0	0
1	26.04	29.64	25.08	19..22	22.14	36.04	42.72	38.76	42.56	37.24
3	36.56	42.79	38.90	34.27	34.56	50.56	61.56	50.86	53.27	47.69
5	58.04	61.38	58.94	59.04	54.67	68.04	73.30	63.88	67.40	58.97
10	74.21	80.81	77.53	80.04	73.52	73.21	90.41	78.35	80.23	79.52
15	94.50	92.50	93.10	95.10	93.12	98.50	99.14	97.95	98.07	97.12

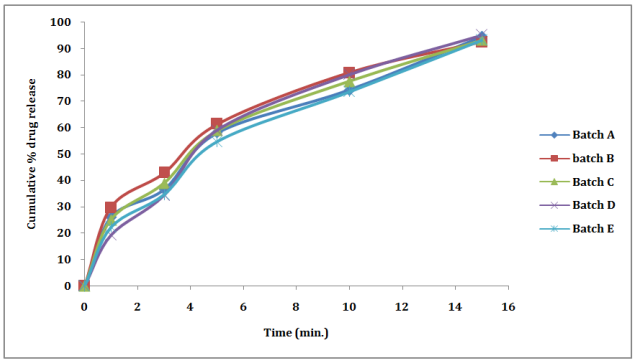

Figure 3: It shows *in vitro* release profile of batch A-E

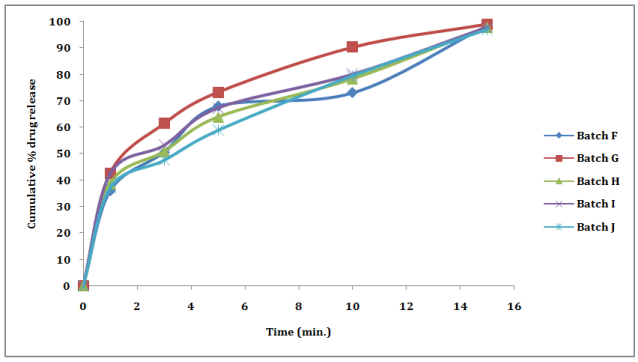

Figure 4: It shows *in vitro* release profile of batch F-J

Comparison with marketed product

Fast dissolving tablets of Tramadol hydrochloride were taken for comparison with marketed tablet **(**Nobligan; 50 mg Tramadol hydrochloride; Sarabhai Chemicals, Ahmedabad).

Drug release profile of marketed product of Tramadol hydrochloride was determined and compared with the best formulation 'G' among the all batches (Table 8).

Table 8: It shows comparative dissolution profile of FDT batch 'G' with conventional marketed product

Time (min)	G	Marketed Product
0	0	0
1	42.72	15.12
3	61.56	28.88
5	73.30	36.52
10	90.41	53.84
15	99.14	65.82
20	-	71.28
25	-	83.91
30		98.024
Coefficient (R^2)	**0.991**	**0.921**

From Table 8, it can be concluded that tablet from formulation 'G' showed more than 95% drug release within 15 minutes while marketed product showed about 68.83% drug release at the same time, and nearly 98% drug release within 30 minutes.Comparative dissolution profile of batch G with marketed product is shown in Fig. 5

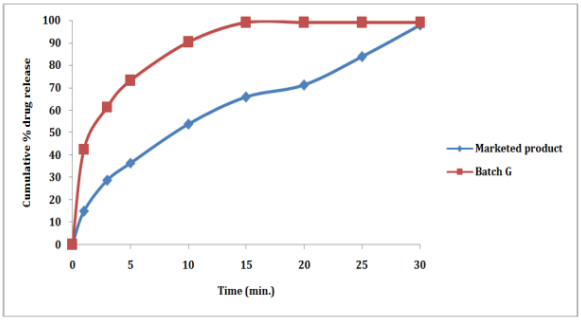

Figure 5: It shows comparative dissolution profile of batch G with marketed product

FDTs of batch 'G' were kept for accelerated stability study at 40 + 2oC and 75 + 5% RH for 1 month in the modified stability chamber. After a period of one month, the samples were observed for any change in physical parameters. Various parameters of FDTs of batch 'G' were evaluated after 15 days and 1 month (Table 9). In vitro release data of FDTs of batch 'G' on zero days, after 15 days and after one month accelerated stability study are tabulated in Table 10.

Table 9: It shows data for evaluation studies of ODTs of batch 'G' after stability

Various Parameters Formulation G	Observation of Tablets for Different Parameters with Respect to Time Elapsed		
	Zero days	After 15 days	After 1 month
Colour	Colourless	Colourless	Colourless
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(sec)	16.07	18.55	17.55

Table 10: It shows *in vitro* release of Tramadol hydrochloride from tablets of on zero days, 15 days samples and after one month accelerated stability studies of 'G'

	Cumulative %Drug Release		
Time in Min	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

CONCLUSION

The conclusion arrived in this article indicated that, the orodispersible tablet of Tramadol hydrochloride prepared in this investigation released drug better than conventional tablet drug release, based on *in vitro* release studies.

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