



Research Article

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF TRAMADOL HYDROCHLORIDE USING NOVEL CO-PROCESSED SUPERDISINTEGRANTS

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ABSTRACT

In the present work, orodispersible tablets of Tramadol hydrochloride were prepared using novel co-processed superdisintegrants consisting of crospovidone and sodium starch glycolate in the different ratios (1:1, 1:2 & 1:3). The developed superdisintegrants were evaluated for angle of repose, Carr's index and Hausner's ratio in comparison with physical mixture of superdisintegrants. The angle of repose of the developed excipients was found to be < 25°, Carr's index in the range of 11-15% and Hausner's ratio in the range of 1.12-1.17. Orodispensible tablets of Tramadol hydrochloride were prepared using the above co-processed superdisintegrants and evaluated for pre-compression and post-compression parameters. Based on in vitro disintegration time (approximately 18 sec), promising formulation CP₁ was tested for in vitro drug release pattern in 0.1N HCl and drug excipients interaction (FT-IR spectroscopy, DSC) were studied. Among the designed formulations, the formulation (CP₁) containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and sodium starch glycolate) emerged as the overall best formulation (t_{50%} 1.46 min) based on drug release characteristics in 0.1N HCl compared to commercial conventional tablet formulation (t_{50%} > 8 min).

Keywords: Tramadol hydrochloride, crospovidone, sodium starch glycolate, co-processed.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily¹. Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medicines as prescribed. The difficulty experienced in particular by pediatrics and geriatrics patients, but this also applies to the patients who are ill in bed or traveling. Other groups that may experience problems using conventional oral dosage form include the mentally ill, developmentally disabled and patients who are uncooperative². Difficulty in swallowing (dysphasia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules. This disorder is associated with different medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders, including cerebral palsy³. Due to a society that is becoming increasingly aged, the development of an appropriate dosage form for the aged patients is most desirable. Because the changes in various physiological functions related with aging including difficulty in swallowing, current dosage forms like capsules are impractical. The most desirable formulation for use by the elderly patients is one that is easy to swallow and easy to handle⁴. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage forms known as orally disintegrating tablets (ODTs) or Fast disintegrating tablets (FDTs) or mouth melting tablets (MMTs) or mouth dissolving tablets (MDTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take water⁵. Orodispensible tablets

(ODT) are solid single-unit dosage forms that are placed in the mouth, allowed to disperse/dissolve in the saliva and then swallowed without the need for water⁶. Orodispensible tablets have been developed, which combine hardness, dosage uniformity, stability and other parameters, with extremely easy administration, since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and traveling patients⁷. In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability. One such approach for improving the functionality of excipients is co-processing of two or more excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual. Co-processing excipients leads to the formulation of excipient granules with superior properties compared with physical mixtures of components or individual components⁸. In the present investigation, the preparation and evaluation of orodispersible tablets by using co-processed superdisintegrants containing crospovidone and sodium starch glycolate was studied. The reasons for selection of crospovidone are high capillary activity, pronounced hydration capacity and little tendency to form gels. Sodium starch glycolate was chosen because of its high swelling capacity. The concept of formulating orodispersible tablets using co-processed superdisintegrants which increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost effective direct compression technique.

MATERIALS & METHODS

Tramadol hydrochloride (TMH) was gift sample from Kopran Pharma Ltd. Mumbai (India). Directly compressible mannitol (Pearlitol SD 200), microcrystalline cellulose (MCC pH -102), sodium starch glycolate, croscopovidone were gifts from Maple biotech, Pune (India). All the other chemicals used were of analytical reagent grade.

CHARACTERIZATION OF DRUG AND EXCIPIENTS⁹

FT-IR spectroscopy

It was employed to ascertain the compatibility between tramadol hydrochloride and the selected polymers. The pure drug and drug with excipients were scanned separately. Potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of tramadol hydrochloride was compared with FT-IR spectrum of tramadol hydrochloride with polymer. Disappearance of tramadol hydrochloride peaks or shifting of peak in any of the spectra was studied.

Differential scanning calorimetry (DSC) Study

DSC analysis of pure drug, and optimized formulation was performed with Shimadzu DSC 60 thermal analyser at the heating flow rates of 5°C per min between 50-300°C under static air using aluminium pans.

Preparation of co-processed superdisintegrants¹⁰

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of croscopovidone and sodium starch glycolate (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44 mesh sieve. The wet granules were dried in a hot air oven at 60° C for 20 minutes. The dried granules were sifted through # 44- mesh sieve and stored in airtight container till further use.

DIRECT COMPRESSION METHOD

Preparation of orodispersible tablets of tramadol hydrochloride by direct compression technique¹¹

All the ingredients were passed through sieve no. 60. Tramadol hydrochloride, mannitol, microcrystalline cellulose and were triturated in a glass mortar. Superdisintegrants were incorporated in the powder mixture and finally magnesium stearate and talc were added as lubricant. The powder mixture was weighed individually and compressed with 7 mm flat face surface punches using GMP multistation (8 station) tablet punching machine. The compressed tablets were then subjected to sublimation at 80°C for 30 min. The tablets were evaluated, optimized formula is given Table1.

Table 1: Formulation of Tramadol hydrochloride (TMH) orodispersible tablets prepared by direct compression method

Ingredients (mg/tab.)	Formulation code						
	CP ₀	PM ₁	PM ₂	PM ₃	CP ₁	CP ₂	CP ₃
Drug*	50	50	50	50	50	50	50
MCC	22	20	20	20	20	20	20
Mannitol	62.5	57.5	57.5	57.5	57.5	57.5	57.5
CP+SSG	-	7	7	7	7	7	7
Aspartame	8	8	8	8	8	8	8
Menthol	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mg.stearate	3	3	3	3	3	3	3
Talc	4	4	4	4	4	4	4
Total (mg)	150	150	150	150	150	150	150

EVALUATION OF ORODISPERSIBLE TABLETS

Hardness test¹²

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm². Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability test¹²

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

$$\text{Friability} = [(\text{Initial weight} - \text{Final weight}) / (\text{Initial weight})] \times 100$$

Weight variation test¹²

The USP weight variation test is run by weighing 20 tablets individually, calculating average weight of the sample, and comparing individual weights with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The percentage deviation in weight variation is allowed mentioned in Table 2.

Table 2: Percentage deviation in weight variation

Average weight of a tablet	Percentage (%) deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

In all the formulations the tablet weight was more than 130mg and less than 324 mg, hence 7.5% maximum difference allowed.

Uniformity of thickness¹²

The crown thickness of individual tablet may be calculated with a micrometer, which permits accurate measurements and provides information on the variation between tablets. Other technique used in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using screw gauge.

Drug content uniformity¹³

Ten tablets are weighed and powdered. An amount of the powder equivalent to 50mg of tramadol hydrochloride content was determined by measuring the absorbance at 271 nm using UV-Visible spectrophotometer (UV 1800- Shimadzu, Japan) after appropriate dilutions.

Wetting time¹⁴

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was measured. Schematic diagram of determination of wetting time is shown in Figure 1.

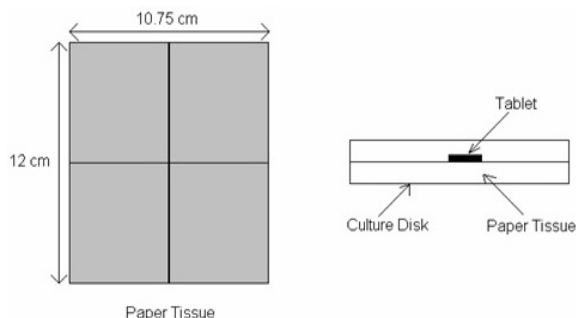


Figure 1: Determination of wetting time

Water absorption ratio¹⁵

A piece of tissue paper folded twice was placed in a small petri dish (Internal diameter = 6 cm) containing 6ml of water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R was calculated using following equation.

$$R = 100 (W_a - W_b) / W_b$$

Where, W_b – weight of tablet before water absorption,
 W_a – weight of tablet after water absorption

Three tablets from each formulation were performed and standard deviation was also determined.

Disintegration test¹⁶

The disintegration time was determined by using USP tablet disintegration test apparatus using 900 ml of distilled water without disk. The time in seconds taken for complete disintegration of the tablets until no mass remaining in the apparatus was measured.

In vitro dissolution studies¹⁷⁻²²

In-vitro dissolution study was performed by using USP type I apparatus (Basket type) [Electrolab Tablet Dissolution Tester] at 100 rpm. 0.1N HCl 900 ml was used as dissolution medium which maintained at $37 \pm 0.5^\circ\text{C}$. Aliquot of dissolution medium (10 ml) was withdrawn at specific time intervals (2,4,6,8,10,12,14,18,22,26,30 min) and then filtered. The amount of drug dissolved was determined by using UV spectrophotometer (Shimadzu, Japan) by measuring the absorbance of the sample at 271.00 nm.

In vitro drug release studies details

Apparatus used : USP type –I dissolution test apparatus
 Dissolution medium : 0.1N HCl.
 Dissolution medium volume : 900 ml
 Temperature : $37 \pm 0.5^\circ\text{C}$
 Speed of basket paddle : 100 rpm
 Sampling intervals : 2,4,6,8,10,12,14,18,22,26,30 min
 Sample withdraw : 10 ml
 Absorbance measured : 271nm.

RESULTS

Characterization of drug and excipients

The FT-IR studies were carried out for pure drug alone and along with polymers as shown in figures 2 and 3 respectively.

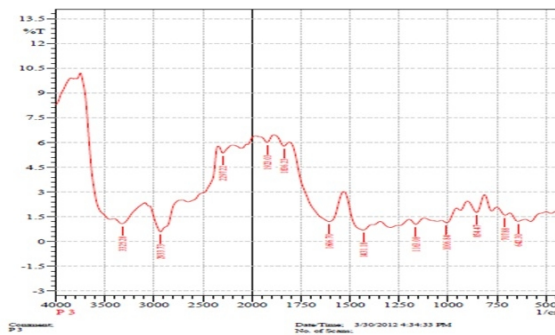


Figure 2: IR spectrum of pure drug

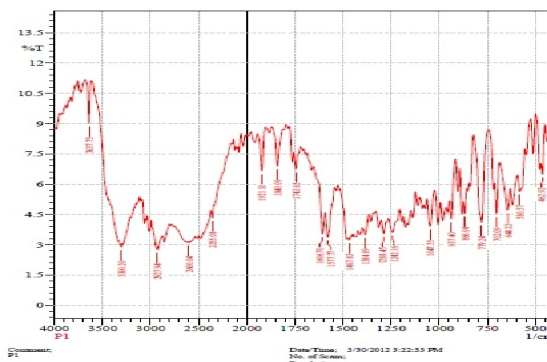


Figure 3: IR spectrum of drug + crosspovidone + sodium starch glycolate

The principal Peaks of drug were not affected and prominently observed in FT-IR spectrum of drug along with polymers i.e. for C-H str 2927.94cm^{-1} to that of pure drug 2933.73cm^{-1} , for N-H str 3300.20cm^{-1} to that of pure drug 3325.28cm^{-1} . This indicates that there is no interaction between tramadol hydrochloride and polymers and the drug was compatible with the formulation components.

DSC studies for pure drug, and optimized formulation 'CP₁' were carried out. The thermo grams are shown in the Figures 4 and 5 respectively.

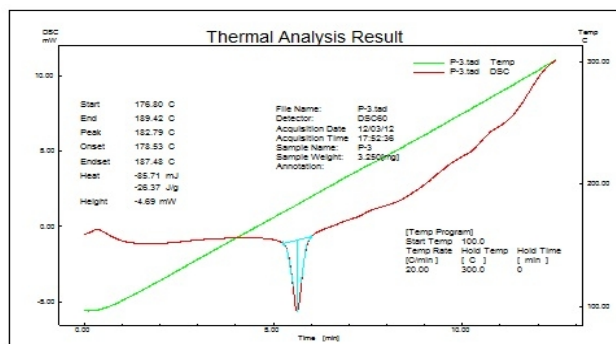
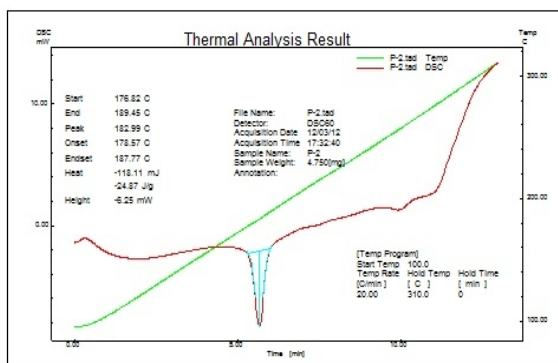


Figure 4: DSC of Tramadol hydrochloride

Figure 5: DSC of optimized formula CP₁

The Figure 4 indicates that the melting of drug has taken place at 182.79°C. It is matching with the literature value 180-184°C. The

Figure 5 indicates that the melting point of the blend (formulation 'CP₁') is 182.99°C. Further no more peaks were found in the Figure 5. This indicates that there is no interaction between drug and excipients. These results are further supported by the results of FT-IR studies.

Co-processed superdisintegrants were prepared by solvent evaporation using croscopovidone and sodium starch glycolate in different ratios (1:1, 1:2, & 1:3). The co-processed superdisintegrants were evaluated for their flow and compression properties in comparison with physical mixture of superdisintegrants. The angle of repose of co-processed superdisintegrants was found to be <25° which indicate excellent flow in comparison to physical mixture of superdisintegrants (>25°) due to granule formation, Carr's index in the range of 11-15% and Hausner's ratio in the range of 1.13-1.17 as shown in Table 3.

Table 3: Results of pre-compression parameters of and physical mixture of superdisintegrants and co-processed superdisintegrants

Parameters	Formulation code					
	PM ₁	PM ₂	PM ₃	CP ₁	CP ₂	CP ₃
Bulk density (gm/cc)	0.500	0.476	0.434	0.588	0.555	0.625
Tapped density (gm/cc)	0.588	0.555	0.500	0.666	0.625	0.714
Angle of repose (degree)	29.14	27.50	25.11	24.44	23.31	22.83
Carr's index (%)	14.96	14.23	13.2	11.81	11.2	12.46
Hausner's ratio	1.17	1.16	1.15	1.13	1.12	1.14

Orodispersible tablets of TMH were prepared using above co-processed superdisintegrants and physical mixture of superdisintegrants. Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance mouth feel. A total of six

formulations and control formulation CP₀ (without superdisintegrant) were designed. As the blends were free flowing (angle of repose <30° and Carr's index <15% as shown in Table 4.

Table 4: Results of pre-compression parameters of TMH ODT formulations prepared by direct compression method

Parameters	Formulation code						
	CP ₀	PM ₁	PM ₂	PM ₃	CP ₁	CP ₂	CP ₃
Bulk density (gm/cc)	0.555	0.588	0.526	0.500	0.625	0.588	0.666
Tapped density (gm/cc)	0.625	0.666	0.625	0.588	0.714	0.666	0.769
Angle of repose (degree)	29.76	28.91	29.45	29.15	27.18	29.3	28.05
Carr's index (%)	11.2	11.71	15.84	15	12.5	11.71	13.42
Hausner's ratio	1.12	1.13	1.18	1.11	1.14	1.13	1.15

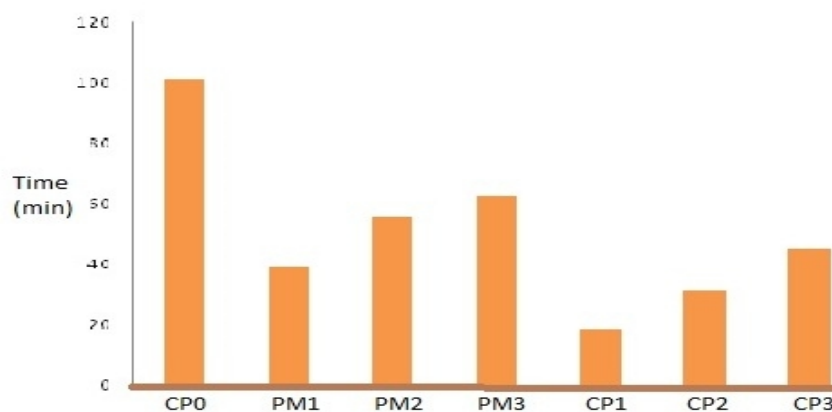
Tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below 7.5%. Drug content was found to be in the range of 98 to 100%, which is within acceptable limits. Hardness of the tablets was found to be in the range of 2.9-3.60 kg/cm². Friability below 1% was an indication of good mechanical resistance of the tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 43-88% and 25-117 sec respectively. Among all the designed formulations, formulation, CP₁ was found to be promising and displayed an *in vitro* disintegration time of 18 sec, which facilitates their faster dispersion in the mouth.

Overall, the formulation CP₁ containing 4% w/w of co-processed superdisintegrant (1:1 mixture of croscopovidone and sodium starch glycolate) was found to be promising and has shown an *in vitro* disintegration time of 18 sec, wetting time of 25 sec and water absorption ratio of 88% when compared to the formulation PM₁ containing 4% w/w of Physical mixture of superdisintegrant (1:1 mixture of croscopovidone and sodium starch glycolate) which shows 39 sec, 43 sec, 78% and control formulation (CP₀) which shows 101sec, 117 sec and 43% values respectively for the above parameters as shown in table 5 and depicted in Figure 6.

Table 5: The results of post-compression parameters of TMH ODT formulations prepared by direct compression method

Parameters	Formulation code						
	CP ₀	PM ₁	PM ₂	PM ₃	CP ₁	CP ₂	CP ₃
Hardness (kg/cm ²)*±SD	3.48±0.04	3.60±0.05	3.31±0.03	3.25±0.08	2.90±0.07	3.21±0.05	3.54±0.08
Friability (%)	0.43	0.63	0.74	0.56	0.60	0.53	0.53
Thickness (mm)*±SD	3.14±0.02	3.13±0.05	3.15±0.04	3.14±0.03	3.18±0.02	3.18±0.02	3.17±0.03
In vitro disintegration time (sec)*±SD	101.33±2.64	39±1.0	55.66±2.08	62.33±1.52	18.66±1.15	31.33±1.15	45±2.64
Wetting Time(sec)*±SD	117.33±4.5	43.33±1.52	59.66±2.5	68.33±1.5	25.33±1.52	41±2.64	49.66±2.08
Water absorption ratio (%)±SD	43.37±1.61	68.25±0.91	60.36±1.40	53.86±0.67	88.08±1.31	64.16±0.43	61.97±0.71
Percent drug content (%)	99.88	98.91	101.24	99.12	99.65	98.18	99.59
Weight variation (%)	142-157 mg (within I.P. limits 7.5%)						

* Average of 3 determinations

Figure 6: *In vitro* dispersion time of tablets from batch CP₀ to CP₃

CP₀ is control formulation, CP₁ is promising orodispersible tablet formulation, PM₁ is formulation containing physical mixture of superdisintegrants in 1:1 ratio, CCF is conventional commercial tablet formulation, D₄ is percent drug released in 4 min, D₈ is percent drug release in 8 min, D₁₂ is percent drug release in 12 min, D₁₆ is percent drug release in 16 min. t_{50%} is time for 50% drug dissolution, t_{90%} is time for 90% drug dissolution.

In vitro dissolution studies on the promising formulation CP₁, control CP₀, PM₁ and commercial conventional formulations (CCF) were carried out in 0.1N HCl, and the various dissolution parameter values viz., percent drug dissolved in 4 min, 8 min and 12 min, 16 min (D₄, D₈ and D₁₂, D₁₈), t_{50%}, and t_{90%} are shown in table 6 and dissolution profile depicted in Figure 7.

Table 6: *In vitro* dissolution parameters in 0.1N HCl

Formulation code	Parameters					
	D ₄	D ₈	D ₁₂	D ₁₈	t _{50%}	t _{90%}
CP ₀	22.20%	40.56%	56.62%	66.54%	10.50 min	>30 min
CCF	30.42%	46.80%	69.10%	83.24%	8.54 min	29.25 min
PM ₁	71.40%	89.63%	96.52%	-	2.07 min	8.03 min
CP ₁	84.25%	99.42%	-	-	1.46 min	5.60 min

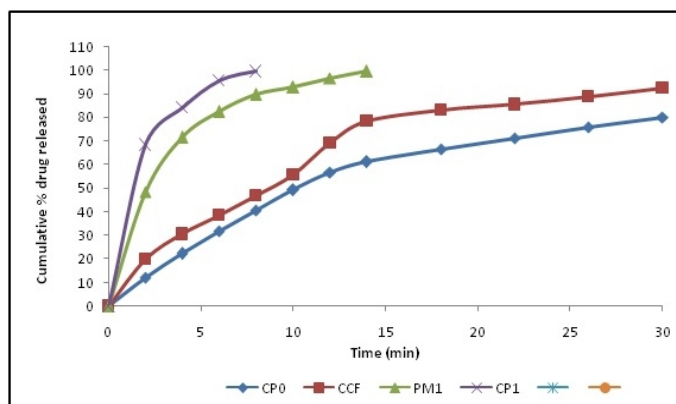


Figure 7: Dissolution rate profiles of (—◆—) control formulation, (—▲—) conventional commercial formulation, (—■—) formulation containing 1:1 physical mixture of crospovidone and sodium starch glycolate, (—×—) promising formulation in 0.1N HCl

This data reveals that overall, the formulation CP₁ has shown nearly six fold faster drug release (t_{50%} 1.46 min) when compared to the commercial conventional tablet formulation of TMH (t_{50%} 8.54 min).

DISCUSSION

From the FT-IR and DSC studies it is clear that there is no interaction between drug and polymers as the principal peaks of pure drug are not affected in IR spectrum of drug along with polymers and no shifting of melting point of drug in optimized formulation of drug. The co-processes superdisintegrants have a

superior flow property as that of the physical mixture of superdisintegrants also the blends formulation shows good flow properties. The CP₁ formulation is the optimized formulation among all the formulation showing better results such as an *in vitro* disintegration time of 18 sec, wetting time of 25 sec and water absorption ratio of 88% when compared to the formulation PM₁ containing 4% w/w of Physical mixture of superdisintegrant (1:1 mixture of crospovidone and sodium starch glycolate) which shows 39 sec, 43 sec, 78% and control formulation (CP₀) which shows 101sec, 117 sec and 43%.

CONCLUSION

In the present work, orodispersible tablets of tramadol hydrochloride were prepared by direct compression using co-processed superdisintegrants such as croscopovidone, sodium starch glycolate in different concentrations.

Based on the above studies following conclusions can be drawn

- From the DSC and FT-IR spectra the interference were verified and found that tramadol hydrochloride did not interfere with the excipients used.
- The co-processed superdisintegrants shows superior flow property and compression characteristics than physical mixture of superdisintegrants.
- Orodispersible tablets of tramadol hydrochloride (CP₁) were successfully prepared using 1:1 mixture of co-processed superdisintegrants i. e. croscopovidone and sodium starch glycolate.
- The tablets were evaluated for pharmacopoeial and non-pharmacopoeial tests. Based on the results, "CP₁" was identified as better formulation amongst all formulations developed for orodispersible tablets.
- The 'CP₁' formulation shows the *in vitro* disintegration time of 18 sec, water absorption ratio of 88% and better drug release.
- The comparative evaluation of orodispersible tablets of tramadol hydrochloride with marketed product suggests that the superdisintegrant addition technique was found to be better compared to conventional tablet available.

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