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RESEARCH ARTICLE

Formulation and Evaluation of Orodispersible Tablets of Tramadol Hydrochloride

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Formulation and evaluation of orodispersible tablets of tramadol hydrochloride

SUMMARY

The rationale of this study is to formulate and evaluate an orodispersible tablet containing an analgesic drug, which when put on tongue disintegrates instantaneously releasing the drug that dissolves or disperses in the saliva generally within < 60seconds. An attempt has been made to develop a novel dosage form aimed to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. Basic approach used in the development of oral dispersible drug delivery system is the use of superdisintegrants. Basic approach used in the development of orodispersible systems is the use of superdisintegrants. Six formulations were designed out of which Formulation F4 shows comparatively good release that is drug release of 91.31%, good hardness, low friability and least wetting time and disintegration time than the other formulations.

Key Words: *Orodispersible, tramadol HCl, drug release, formulations*

Tramadol hidroklorid'in ağızda dağılan tablet formülasyonu ve değerlendirilmesi

ÖZET

Bu çalışmanın gerekçesi, analjezik bir etkin maddenin, dil üzerine konduğunda, hemen dağılan ve tükrükte çözünerek veya dağılarak genelikle 60 sn'den kısa sürede salımını yapan, ağızda dağılan tablet formülasyonunu hazırlamak ve değerlendirmektir. İlaç moleküllerinin güvenilirliğini, etkinliğini ve hasta uyuncunu artırmayı amaçlayan yeni bir dozaj şekli geliştirilmesine yönelik bir girişimde bulunulmuştur. Ağızda dağılan tablet formülasyonunun geliştirilmesinde temel yaklaşım, süper dağıtıcıların kullanılmasıdır. Süper dağıtıcıların kullanılması, ağızda dağılan sistemlerin geliştirilmesindeki temel yaklaşımdır. Çalışmada altı formülasyon tasarlanmış, formülasyon F4 diğer formülasyonlarla kıyaslandığında, daha iyi ilaç salımı %91.31, daha iyi sertlik, daha düşük ufalanabilirlik göstermiş, en az ıslanma ve dağılma sürelerine sahip olduğu bulunmuştur.

Anahtar kelimeler: *Ağızda dağılan, tramadol HCl, ilaç salımı, formülasyonlar*

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INTRODUCTION

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly the patient compliance (1). The most popular solid dosage form is tablet. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by the oral route. If it cannot, the drug is primarily relegated to administration in a hospital setting or physician's office. If patient self administration cannot be achieved, the sales of the drug constitute only a small fraction of what the market would be otherwise. Tablets are unit dosage forms in which one usual dose of the drug has been accurately placed. The tablet has a number of advantages (2). One of the major advantages of tablet over capsules, which has recently proved significant, is that the tablet is an essentially tamperproof dosage form. One important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking of water plays an important role in the swallowing of oral dosage forms. Often, people experience inconvenience in swallowing. Conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis (3). Recent advances in Novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is orodispersible tablet (ODT). Orodispersible tablets (ODT) are not only indicated for people who have swallowing difficulties, but are also ideal for active people. Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablets etc (4). Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. 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 tablets dosage form. The advantage of oral dispersible dosage forms are increasingly being recognized in both, industry and academics (5). Their growing importance was underlined recently when European pharmacopoeia adopted the term —Orodispersible tablet as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. According to European pharmacopoeia, the Orodispersible Tablet should disperse/disintegrate in less than three minutes. The basic approach in development of ODT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel,explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in to the saliva (6). The bioavailability of some drugs may be increased due to absorption of drug 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 tablet. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, tablet compression, and disintegration addition (7). Tramadol hydrochloride is taken by mouth with or without food. Tramadol hydrochloride is one of a group of medicines called centrally acting analgesics and is used for relief of moderate or severe pain. If it is taken as immediate-release oral formulation the onset of pain relief occurs within about an hour.

MATERIAL AND METHODS

Tramadol hydrochloride was obtained as a gift sample from Litaka pharmaceuticals, pune.All other ingredients were of analytical grade.

Preparation of Orodispersible Tablets of Tramadol hydrochloride by Superdisintegrant addition method (8).

Development of the formulation in the present study was mainly based on the type of disintegrant, concentration of polymers, and the drug. Various polymers and excipients in different combinations were used so as to get tablet with good physical properties. Tramadol hydrochloride is water soluble drug, and dose was taken 50 mg. So, in the present study attempts were made to get good physical and release profile of the tablets (Table 1) (9).

Table 1. Compositions for ODT of Tramadol hydrochloride by Superdisintegrant Addition Method

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6
Drug (equivalent to tramadol HCl 50mg)	50	50	50	50	50	50
Sodium starch glycolate	5	10	-	-	-	-
Crosspovidone	-	-	5	10	-	-
Pregelatinized starch	-	-	-	-	5	10
Microcrystalline cellulose	82	82	82	82	82	82
Aspartame	7	7	7	7	7	7
Mannitol	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium Stearate	2	2	2	2	2	2
Talc	4	4	4	4	4	4
Starch	10	10	10	10	10	10
Total (mg)	200	200	200	200	200	200

Tablets Prepared by superdisintegrant addition method

In this superdisintegrant addition method, all the excipients and drug were geometrically mixed and that blend was directly used for compression. Different disintegrants were used in different concentrations to get good orodispersible tablets of Tramadol hydrochloride. Different excipients like direct compressible excipients, lubricants, and glidants were used to get the tablets with acceptable physical properties (10). Here, the weight of all tablets was maintained constant i.e. 200 mg to minimize the effect of surface area/volume on the drug release pattern. Automatic press machine was used for tabletting. Model number of tablet punching machine used was DB3D-27 (Riddhi Pharma Machinery Limited, INDIA). The applied compression pressure was 100 MPa. Punch diameter was 30.16 mm.

Preformulation Studies

Melting Point: Hirschmann® melting point apparatus was used for determination of melting point. Company for melting point device used was Sigma-Aldrich and model number was Aldrich-Z611174 and country manufacturer was India. Melting point of Tramadol hydrochloride was determined by capillary tube method and it was found to be 183 ± 0 .59 (n = 3). DSC studies for pure drug and optimized formulation

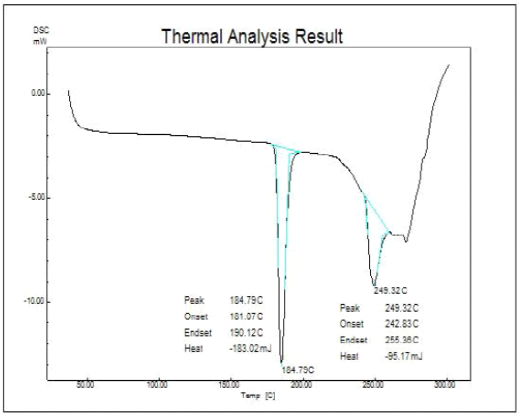

Figure 1. DSC of Tramadol hydrochloride

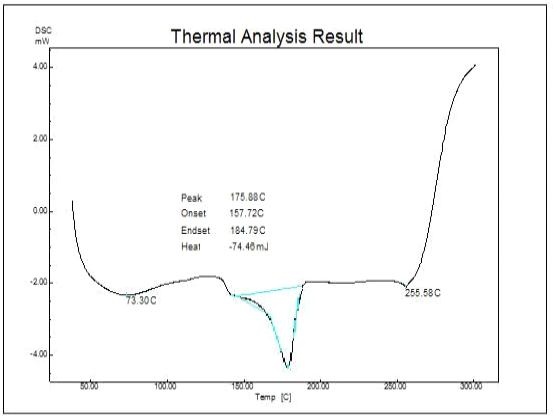

Figure 2. DSC of optimized formula

were carried out. The thermo grams are shown in the Figures 1 and 2 respectively for pure drug and optimized formula, it indicates that the melting of drug has taken place at 184.79 °C. It is matching with the literature value 184 °C. Melting point of the blend (formulation) is 175.88 °C. Before the excipients completely melts, the drug might have started melting giving the broad peak that is 175.88 °C. Further no more peaks were found in the Figure 2. This indicates that there is no. interaction between drug and excipients.

Drug – Excipients Compatibility Studies

Shimadzu apparatus (model No.3116465) was used for determination of FTIR.FT-IR studies were carried out for pure drug alone and along with polymers (11) An FT-IR spectrum of pure Tramadol hydrochloride was shown in the Figure 3 and peaks were listed in the Table 2. Similarly FT-IR spectra of Tramadol hydrochloride in combination with polymers and in optimized formulation were shown in Figures 4 to 6. The peaks are given in the Table 2 can be considered as characteristic peaks of Tramadol hydrochloride. This indicates that there is no interaction between Tramadol hydrochloride and polymers and the drug was compatible with the formulation components.

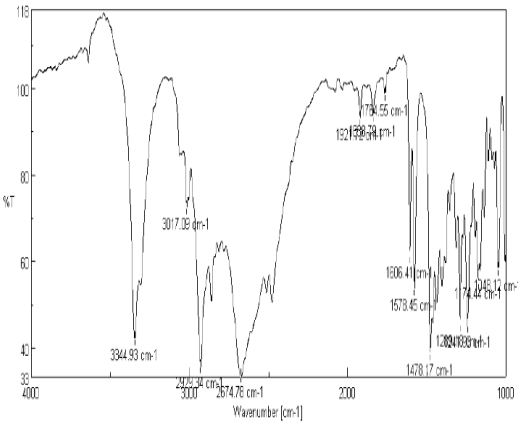

Figure 3. FTIR Spectrum of Tramadol

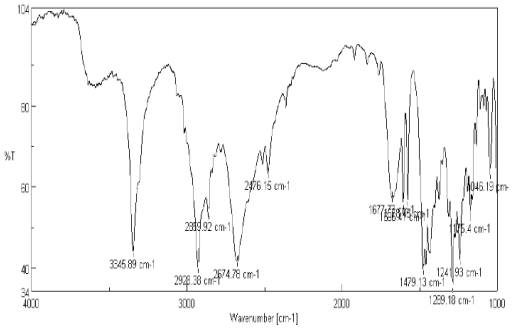

Figure 4. FTIR Spectrum of Drug and rospovidone Physical hydrochloride Mixture

Table 2. Data obtained for IR spectra of Tramadol hydrochloride along with excipients

Functional Group	C-H str (aromatic)	C-H str (aliphatic)	N-H str	C-N str	C=C str	C-O str
Pure dug	2929.34	2674.78	3344.93	1289.4	1606.41	1202.9
Drug and CP	2928.38	2674.78	3345.89	1241.93	1677.77	1175.4
Drug and MCC	2929.34	2671.89	3303.46	1289.18	1606.41	1051.98

Drug: Tramadol hydrochloride, CP: Crospovidone, MCC: microcrystalline cellulose

Table 3. Physical Properties of Tablet blend

Code of Formulations	Angle of Repose	Bulk density (g/ml)	Tapped density	Carr's Index (%)	Hausner Ratio
F1	27.54	0.4186	0.4866	13.97	1.16
F2	28.32	0.3750	0.4391	14.56	1.16
F3	25.36	0.4235	0.4933	14.13	1.16
F4	26.65	0.3873	0.4505	13.98	1.16
F5	27.58	0.3790	0.4395	13.70	1.15
F6	27.28	0.3956	0.4676	15.37	1.18

Table 4. Evaluation Studies of Compressed Tablet of Tramadol Hydrochloride

Formulation code	Weight Variation (%)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)	Disintergration time (sec.)	Wetting time (sec.)	Drug Content (%)
F1	200.3	0.402	3.66	3.19	7.98	57.66	54	98.52
F2	201.5	0.530	3.83	3.21	7.97	48.33	38	98.82
F3	201.5	0.785	3.16	3.18	8.00	27	23	98.23
F4	200.5	0.656	3.16	3.19	7.99	17.66	18	100.29
F5	200.9	0.658	3.66	3.21	7.98	167	96	98.23
F6	200.9	0.662	4.16	3.20	8.00	150.3	87	99.66

Evaluation of blends of tramadol

The blends obtained were evaluated for blend properties and are given in Table 3.

Angle of Repose

A glass funnel was placed with a clamp on a ring support over a glass plate. The glass plate was placed on a micro –lab jack. Approximately 100 g of powder was transferred into the funnel keeping the orifice blocked by the thumb. As the thumb was removed, the lab-jack was adjusted so as to lower the plate and maintained a 6.4 mm gap between the bottom of the funnel stem and top of powder pile. When the powder was emptied from the funnel, the angle of heap to the horizontal plane was measured by a protractor. Angle of repose for the formulated blend was carried out (12) and the results were shown in Table 3. The angle of repose for the formulated blend was carried out (12) and the results were shown in Table no 3. It concludes that the entire formulations blends were found to be in the ranges from 25^0.36' to 27.58', which indicates good flow property of blends.

Carr's Index

For measuring bulk density bulk density apparatus was used (Edutek Instrumentation, Ambala city, India). Powder was passed through a standard sieve number 20. A weighed amount (approximately 50 g) was introduced into a 100 ml graduated cylinder. The cylinder was fixed on the bulk density apparatus and timer knob was set for 100 tappings. The volume occupied by the powder was noted. The final volume was noted as bulk volume. Carr's index was carried out and found to be between13.70% to 15.37%. The results shown in Table 3 indicate the powder blends have the required flow property for compression.

Carr's index= Tapped density-Bulk density/Tapped density*100

Hausner's Ratio

Hausner's ratio was carried out and found to be between 1.15 to 1.18.The results shown in Table 3 indicated the powder blends have good flow properties for compression**.**

Hausner ratio=Tapped density/Bulk density

Evaluation of compressed tablets of tramadol hydrochloride

Tablets of tramadol hydrochloride of 200 mg were punched and subjected to evaluation studies such as weight variation, hardness, friability, and thickness, diameter, wetting time, disintegration and drug content. The results of the evaluation studies are shown in Table 4.

Evaluation of tablets (13)

Shape of the tablets

Microscopic examinations of tablets of all formulation were found to be circular in shape with no cracks and white in color.

Thickness of tablets

The thickness of the all formulation was found to be between 3.18 to 3.21 mm as shown in Table 4.

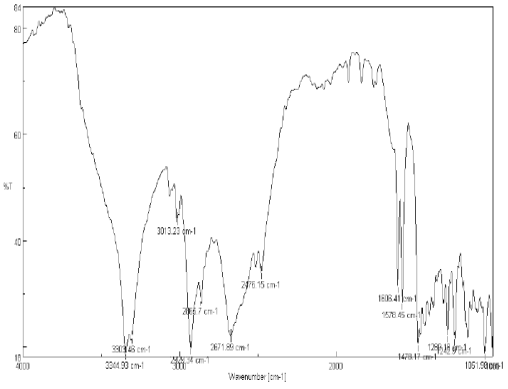

Figure 5. IR Spectrum of Drug and MCC

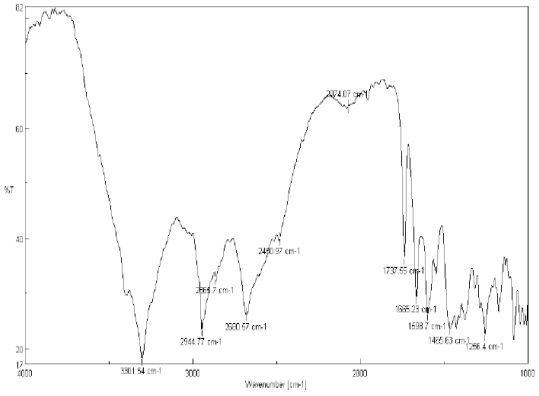

Figure 6. IR Spectrum of Optimized formulation physical mixture

Diameter of tablets

Diameters of all the formulations were found between to be 7.97 to 8.00 mm as shown in Table 4.

Hardness test

Monsanto and pfizer tester were used for measuring hardness. The measured hardness of tablets of each batch ranged between 3.16 to 4.16 kg/cm^2 of formulations as shown in Table 4 This ensures good handling characteristics of all batches.

Friability test

Roche friability apparatus was used for friability measurement. The values of friability test were tabulated in Table 4. It is ranging from 0.402 to 0.785 the % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Weight variation test

The percentage weight variations for all formulations were tabulated in Table 4. All the formulated tablets passed weight variation test, as the % weight variation was within the pharmacopoeial limits of 7.5% of the average weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Drug content uniformity

Drug content was determined by UV method. Absorbance maxima of tramadol hydrochloride was shown at 271 nm. It is shown in figure 8. Buffer was used as medium, drug content was calculated individually by extracting the drug from tablets. The drug sample was analysed at 271 nm, m value was 0.0617, r value was 0.9991. The percentage of drug content was found to be 98.23% to 100.29% of tramadol. It complies with official specifications. The results were shown in Table 4.

Disintegration test

The values of disintegration test for tramadol tablets were tabulated in Table 4. The results of *in-vitro* disintegration time of all the tablets were found to be within the prescribe limits and satisfy the criteria of oral dispersible tablets. In the formulation F1 to F6, formulations with different superdisintegrant in different concentration were used. Among the six superdisintegrant crospovidone showed the highest efficiency. It was observed that at lower concentration (2.5% crospovidone) showed the least disintegration time as compared to 5% crospovidone. Such a behaviour of superdisintegrants at higher concentration may be due to the blockade of capillary pores, which prevents the entry of fluid into the tablet.

Wetting time

The wetting time for all the formulation was tabulated in Table 4. The value lies between 18sec to 96 sec.

Cumulative percentage drug release

All the formulations of prepared oral dispersible tablets of tramadol were subjected to *in vitro* release studies using dissolution apparatus in 6.8 pH buffer. The release data obtained for all the formulations were tabulated in Table 5 and Fig 7 shows the plot of cumulative % drug released as a function of time for different formulations. In the formulation F1 to F6, formulation F4 containing 5% crospovidone shows the better drug release of 98.93% at the end of 4 min.

Table 5. *In Vitro* Dissolution Profile of F1-F6

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	2.19±0.140	31.49±0.6409	46.18±0.760	50.25±0.780	4.67±0.240	11.77±0.288
4	51.16±0.698	59.06±0.7012	93.04±0.9780	98.93±0.9989	9.58±0.378	18.32±0.3189
6	72.63±0.799	73.43±0.801	97.44±0.989	97.17±0.978	13.41±0.314	20.41±0.378
8	85.97±0.819	86.52±0.829	96.64±0.979	95.41±0.965	23.78±0.514	31.60±0.6509
10	91.14±0.910	93.27±0.939	96.04±0.969	94.05±0.944	36.38±0.315	47.72±0.678
12	92.93±0.929	91.88±0.928	95.44±0.929	93.07±0.942	51.09±0.706	63.98±0.808
15	91.34±0.919	90.89±0.908	95.04±0.909	91.31±0.910	63.29±0.808	81.18±0.818

Table 6. Stability Study of Selected Formulation F4

Formulation	Sampling Intervals (days)	Physical Appearance	Drug Content (%)	Friability (%)	Hardness (kg/cm²)	Cum % drug release
F4	0	No change	99.29	0.656	3.16	98.93
F4	15	No change	99.29	0.656	3.16	98.93
F4	30	No change	99.29	0.656	3.16	98.93
F4	45	No change	99.29	0.656	3.16	98.93
F4	60	No change	99.29	0.656	3.16	98.93
F4	180	No change	99.29	0.656	3.16	98.93

indicating good bioavailability of the drug from this formulation. The result of the study shows that increase in the concentration of superdisintegrant, there is increase in cumulative % drug release.

Stability study

Stability studies of the formulations were carried out as per the ICH guidelines (14). The optimization formulation F4 was subjected to stability studies at 40° C and 75% RH for a period of 6 months. The physical stability was assessed by the appearance and the chemical stability by change in the drug content. The results showed (Table 6) that the formulation were stable at the end of the 6th month.

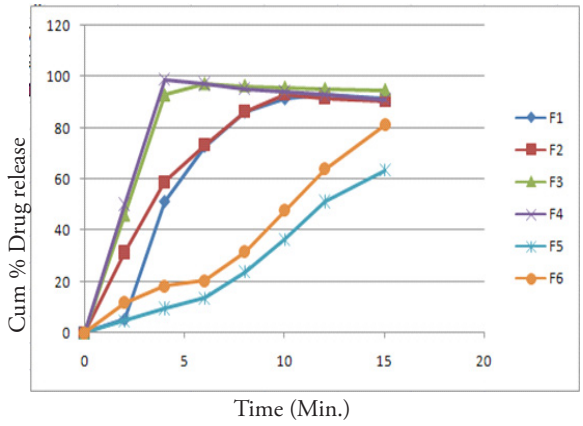

Figure 7. In Vitro Dissolution Profile of F1 F6

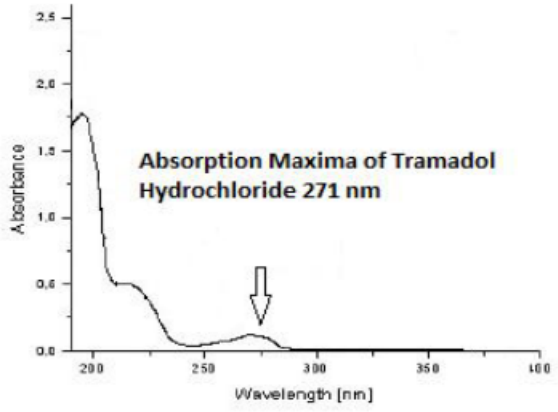

Figure 8. Absorbance maxima of Tramadol hydrochloride in buffer

RESULTS

No interference due to additives in the estimation of tramadol hydrochloride was observed. Different superdisintegrants were used to get formulations of orodispersible tablets by superdisintegrant addition method and finally one batch of tablets containing crosspovidone was optimized. Tablets were evaluated for pharmacopoeial and non pharmacopoeial tests and were found to be within the prescribed limits. *In vitro* release profiles of optimized formulations of Tramadol hydrochloride orodispersible tablets (F4) released 91.31% within 15 min. and *in vitro* dispersion time was found to be 17 sec. Formulation was found to be stable for one month under accelerated stability conditions.

CONCLUSION

Oral dispersible tablets of Tramadol hydrochloride using super disintegrating agents were found to be good without chipping, capping and sticking.

The drug content was uniform in all the formulations of tablets prepared.

Infrared spectroscopic studies indicated that the drug is compatible with the polymers.

The drug, superdisinegrating agent ratio was found to influence the release of drug from the formulations. As the level of superdisinegrating agent is increased, the drug release rates were found to be increased.

Formulation F4 shows comparatively good release, good hardness, low friability and least wetting time and disintegration time than the other formulations.

From the study, it can be concluded that direct compression method showed better disintegration.

The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability.

Administration of conventional tablets of Tramadol HCl has been reported to exhibit fluctuations in the plasma drug levels resulting in either manifestation of side effects or reduction in drug concentration at the receptor site. Advantages of oral dispersible tablet will surely enhance the patient compliance, low dosing, rapid onset of action and fewer side effects.

It was concluded that oral dispersible tablets of Tramadol HCl can be prepared successfully as it satisfies all the criteria as an oral dispersible tablet and would be alternative to the currently available conventional tablets.

Prepared formulations were stable during 180 days storage period at controlled 40°C and 75% RH.

REFERENCE

1. Swamy PV, Divate SP, Shirsand SB, Rajendra P. Preparation and evaluation of orodispersible tablets of pheniramine maleate by effervescent method. *Indian J Pharm Sci.*71 (2) :151-154,2009
2. Shahi SR, Agrawal GR, Shinde NV, Shaikh SA, Shaikh SS, Somani VG.Formulation And *In Vitro* Evaluation Of Oro-Dispersible Tablets Of Etoricoxib With Emphasis On Comparative Functionality Evaluation Of Three Classes Of Superdisintegrants. *RJC Rasayan J Chem.*1 (2) :292-300,2008
3. Balmuralidhara V, Sreenivas SA, Gangadharappa HV, Pramodkumar TM. Investigation on the Effect of different disintigrants on the orodispersible tablets of rabeprazole. *Asian journal of scientific Research.*2 (4): 190-197,2009
4. Kuchekar BS, Badhan AC, Mahajan HS. Tablets: A novel drug delivery system. *Pharma Times.*35: 7-9,2003
5. Bhowmik D, Chiranjib B, Krishnakant, Pankaj, Chandira RM(2009). Fast Dissolving Tablet: An Overview.*Journal of Chemical and Pharmaceutical Research.*1 (1) :163-77,2009
6. Prajapati BG, Ratnakar N.A. Review on Recent patents on Fast Dissolving DrugDelivery System. *International Journal of PharmTech Research.*1 (3):790-8,2009
7. Shukla D, Chakraborty S, Singh S, Mishra B. Tablets I: An Overview of Formulation Technology. *Sci Pharm.*77: 309-26,2009
8. Bhardwaj S, Jain V, Sharma S, Jat RC, Jain S. Orally disintegrating tablets: a review. *Drug invention today.*2(1):81-88,2010
9. Mizumoto T, Masuda Y, Yamamoto T, Yonemochi E, Terada K. Formulation design of a novel fast-disintegrating tablet. *International Journal of Pharmaceutics.*306: 83–90,2005.
10. Okuda Y, Irisawaa Y, Okimoto K, Osawa T, Yamashitab S.A new formulation for orally disintegrating tablets using a suspension spray-coating method. *International Journal of Pharmaceutics.*382:80–87,2009.
11. Fukami J, Yonemochi E, Yoshihashi Y, Terada K. Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose. *International Journal of Pharmaceutics*. 310:101–9,2006.
12. AlHusban F, Perrie Y, Afzal RM.Formulation and characterisation of lyophilised rapid disintegrating tablets using amino acids as matrix forming agents.*European Journal of Pharmaceutics and Biopharmaceutics.*75: 254–62,2010.
13. Aldelbary G, Prinderre P, Eouani C, Joachim J, Reynier JP, Piccerelle P. The preparation of orally disintegrating tablets using a hydrophilic waxy binder. *International Journal of Pharmaceutics.*278:423–33,2004.
14. Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. *European Journal of Pharmaceutical Sciences.*15:295–305,2002.