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Design, Development and Evaluation of Oral Dispersible Tablets of Tramadol Hydrocloride

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ABSTRACT:

The aim of this study is to develop a pharmaceutical stable formulation of an orally dispersible tablet of tramadol hydrochloride. In this study, orally dispersible tablets of tramadol hydrochloride were prepared by direct compression method. For optimization and development of a robust formulation, several test formulations were taken, i.e. from F1-F9. The study is to clarify the effect of different super disintegrants such as crospovidone (CP) (F1, F2, F3), croscarmellose sodium (CCS) (F4, F5, F6), sodium starch glycolate (SSG) (F7, F8, F9) on the disintegration and dissolution properties of the drug. Weight variation, wetting time, hardness, thickness, friability, % drug content, disintegration time, in vitro drug release and in vivo release studies were evaluated for the prepared tablets. Formulation F3 showed a drug release of 99.18% in 30 minutes, which is faster than the other 2 super disintegrants used in the study as well as the innovator product. Stability studies showed that formulation F3 was sufficiently stable at 40°C / 75% RH for 1 month. From the result of the study formulation F3 is more stable.

Key words: Tramadol hydrochloride, crospovidone, Croscarmellose sodium, Sodium starch glycolate, In-Vitro drug release, In-vivo drug release.

1. INTRODUCTION

An perfect dosage routine in the drug remedy of any disorder is the one, which right away attains the want therapeutics attention of drug in plasma(or at the website of action) and keeps it steady for the whole length of treatment1. Drugs are often taken with the aid of oral administration, even though a few capsules taken orally are supposed to be dissolved inside the mouth, majority of capsules taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered as most natural, convenient means of administering drugs[2]. Oral dispersible pill is an progressive pill technological know-how the place the dosage shape containing lively pharmaceutical components disintegrates rapidly, normally in a count number of seconds, barring the want for water, imparting foremost comfort to the patient[3,4]. Tramadol and its metabolite (M1) are selective, vulnerable OP3-receptor agonists. Opiate receptors are coupled with G- protein receptors and characteristic as each fantastic and terrible regulators of synaptic transmission by means of G-proteins that set off effector proteins. As the effector device is adenylate cyclase and cAMP placed at the internal floor of the plasma membrane, opioids reduce intracellular cAMP with the aid of inhibiting adenylate cyclase. Subsequently, the launch of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline is inhibited. The most typically stated destructive drug reactions are nausea, vomiting, sweating and constipation[2].

2. MATERIAL AND METHODS

Tramadol hydrochloride, Micro crystalline cellulose, sodium starch glycolate, crospovidone, Croscarmellose sodium, Aspartame were obtained as gift sample from KAPL, Bangalore. Other materials used were purchased from local vendor.

3. EXPERIMENTAL WORK

Formulation of Tramadol hydrochloride Tablets:

A combination of Tramadol HCl and β-cyclodextrin (1:2) used to be floor in a glass container and a minimal quantity of water was once brought and triturated for 15-30min to get the slurry and air dried at 40◦c for 24hrs, pulverized and exceeded via sieve no:100 and saved in a desiccator over fused calcium chloride. The mixture was used for the preparation of tablets, all materials were passed through sieve no.40. Disintegrant was divided into two equal parts by weight. Drug complex was added to one part, and in another part aspartame was added. Then the materials were blended for 10mins.Then the Blended mass were sifted through 20/40 mesh screen. Ten percent of the fines were added to the mass and then blended for another 2

minutes. Then a weighted quantity of Aerosil and remaining super disintegrant were added to the mass and blended for five minutes. The granules of the drug were compressed in a 16 station rotary compression machine using flat faced punches of 10mm diameter.

Table 1: Composition of Oral Dispersible tablet of Tramadol HCL (All quantities in mg)

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug complex	151.2	151.2	151.2	151.2	151.2	151.2	151.2	151.2	151.2
Micro crystalline cellulose	116.3	110.3	104.3	116.3	110.3	104.3	116.3	110.3	104.3
Crospovidone	12	18	24	_	_	_	_	_	_
Croscarmellose	_	_	_	12	18	24	_	_	_
Sodium starch glycolate	_	_	_	_	_	_	12	18	24
Aspartame	6	6	6	6	6	6	6	6	6
Aerosil	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Talc	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mint flavour	3	3	3	3	3	3	3	3	3
Total weight of the tablet	300	300	300	300	300	300	300	300	300

volume (Vo) weight of powder (W). The bulk density was calculated using the formula.

Bulk Density (B.D) = W / Vo

Tapped Density:

The measuring cylinder containing known mass of blend was tapped for a fixed number of taps. The minimum volume (Vf) occupied in the cylinder and the weight of powder (W) was measured. The tapped density was calculated using the formula.

Tapped Density (T.D) = W / Vf

Angle of repose:

Angle of repose (a) was once decided with the aid of the usage of funnel method. The mixture used to be poured thru a funnel that can be raised vertically till a most cone peak (h) was once obtained. The radius of the heap (r) was once measured and attitude of repose was once calculated.

$a = \tan^{-1}(h/r)$

Compressibility index:

The simplest way measurement of free flow property of powder is compressibility, an indication of ease with which a material can be induced to flow is given by % compressibility, which is calculated as follows:

C = [(T.D-B.D) / T.D] x 100

Where T.D and B.D are bulk density and tap density respectively.

Hausner's ratio:

Hausner's ratio is an index of ease of powder flow; it calculated as follows:

Hausner's ratio = T.D / B.D

Where T.D and B.D are bulk density and tap density respectively.

Evaluation of tablets:

All the tablets were evaluated for different parameters like hardness, thickness, friability, wetting time, drug content, disintegration time in- vitro drug Release and In-Vivo studies.

Hardness: For each formulation hardness was tested using the Pfizer hardness tester (Cadmach, India)

Friability:

Twenty pills have been weighed and positioned in Roche friabilator (Electrolab, Mumbai) and equipment was once circled at 25 rpm for four min. After revolution capsules had been dusted and weighed [1, 2]. The friability is given by means of the formula:

F = [1- Wo / W] x 100

Where, Wo = weight of the tablets before the test, W = weight of the tablets after the test.

Drug content:

Finely powder no longer fewer than 20 tablets. Transfer a component of the powder, equivalent to 50mg of tramadol hydrochloride, and transferred to a 100ml volumetric flask; the quantity was once made-up with 0.1 N HCl and sonicated for 30 min to smash the complex. The samples have been filtered via Whatman filter paper No. 41, diluted suitably and absorbance used to be measured at 272 nm.

Wetting Time

A Petri dish containing 6 ml of distilled water used to be used. A tissue paper folded twice used to be stored in the dish and a pill was once positioned on it. A small volume of amaranth crimson coloration was once put on the higher floor of the tablet. Time required for the top floor of the pill to grow to be pink was once referred to as the wetting time of the tablet

Disintegration time:

The in-vitro disintegration time was once decided by using the usage of disintegration check apparatus. One pill used to be positioned in every of the six tubes of the equipment and one disc used to be brought to every tube. The time in seconds taken for whole disintegration of the pill with no palpable mass in the equipment was once measured in seconds.

In vitro drug release:

The In vitro dissolution check used to be carried out the use of USP Type II dissolution check equipment at 37±2°C and 50 rpm speed. 900 ml of 0.1 N HCl used to be used as dissolution medium. Aliquot equal to 10 ml used to be withdrawn at precise time intervals and quantity of Tramadol launched from tabletwas determined.

Release Kinetics

The results of In-vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows5,6,7

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchis model)
3. Cumulative percent drug release versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (korsmeyers model)

4. STABILITY STUDIES:

The cause of balance checking out is to grant proof on how the high-quality of a drug substance or drug product varies with time below the affect of a range of environmental elements such as temperature, humidity and light, and permits endorsed storage prerequisites and shelf lives to be established. In the present study,

The stability studies were carried out as per ICH guidelines 40◦C ± 20◦C / 75% ± 5% RH for the selected formulation F3 for 1 month. After specified time intervals, parameters like physical appearance, disintegration time, drug content, and dissolution were evaluated according to the procedure described as earlier.

In vivo Studies [8,9]

Healthy Adult rabbits were used for the study. Physical examinations and plasma biochemical analyses had been carried out to make sure rabbits had been healthful prior to the experiment. One blood pattern was once gathered earlier than therapy with tramadol thru marginal ear vein. Then, tramadol was once administered once, and blood samples had been accumulated at a range of time factors up to 6hrs after administration. Blood samples have been analyzed with excessive overall performance liquid chromatography to decide plasma concentrations of tramadol.

5. RESULTS AND DISCUSSION:

Table 2: Evaluation of precompressed granules of Tramadol HCL

Formulation	Bulk density (gm/cc) ±SD	Tapped density (gm/cc) ±SD	Compressibility index (%) ±SD	Hausner's ratio (%)±SD	Angle of repose(□) ±SD
F1	0.289±0.023	0.344±0.03	13.47±0.002	1.155±0.04	21.98±0.03
F2	0.309±0.021	0.348±0.012	11.02±0.03	1.126±0.01	20.43±0.04
F3	0.296±0.012	0.321±0.02	7.78±0.001	1.084±0.03	19.69±0.02
F4	0.293±0.023	0.316±0.023	7.27±0.012	1.078±0.01	20.79±0.05
F5	0.312±0.032	0.375±0.012	16.80±0.023	1.201±0.02	22.31±0.04
F6	0.295±0.014	0.342±0.021	13.74±0.023	1.159±0.31	21.01±0.21
F7	0.307±0.032	0.370±0.021	17.02±0.001	1.205±0.01	22.24±0.04
F8	0.281±0.041	0.324±0.012	13.27±0.001	1.153±0.02	19.76±0.03
F9	0.318±.021	0.347±0.024	8.35±0.002	1.091±0.03	21.47±0.05

Table 3: Evaluation of Compressed Granules of Tramadol Hydrochloride

Formulation	Weight Variation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	299±0.14	3.48±0.12	3.62± 0.016	0.462
F2	305±0.25	5.65±0.11	3.14±0.012	0.501
F3	301±0.01	4.53±0.14	3.42±0.01	0.442
F4	305±0.43	3.51±0.12	4.14±0.14	0.364
F5	304±0.38	4.21±0.14	3.27±0.03	0.409
F6	302±0.24	4.04±0.15	4.01±0.02	0.486
F7	298±0.18	4.79±0.14	3.93±0.12	0.423
F8	304±0.16	4.23±0.16	3.76±0.01	0.412
F9	306±0.41	4.54±0.13	4.15±0.13	0.389

Table 4: Evaluation of Compressed Granules of Tramadol Hydrochloride

Formulation	Wetting Time (sec)	Disintegrating Time (sec)	Drug content (%)
F1	75	31	98.23
F2	41	24	98.76
F3	23	18	99.12
F4	29	20	101.76
F5	30	27	100.14
F6	35	29	98.99
F7	29	32	99.01
F8	31	27	98.66
F9	27	26	98.41

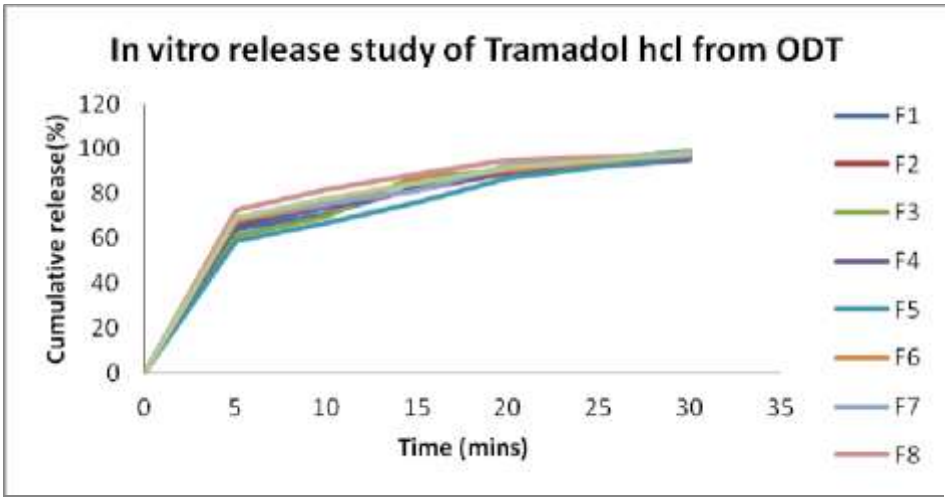

Figure 1*: Invitro* Dissolution Profile of Tramadol HCl from ODTs (F1-F9)

Determination of Release Kinetics:

Table 5: Kinetic Studies of Oral Dispersible Tablets

Release kinetics	**R2**	**Intercept**	**Slope**
Zero order	0.971	54.48	1.573
First order	0.908	2.142	0.067
Higuchi	0.982	32.33	12.31
Korsmeyer peppas	0.972	1.577	0.280

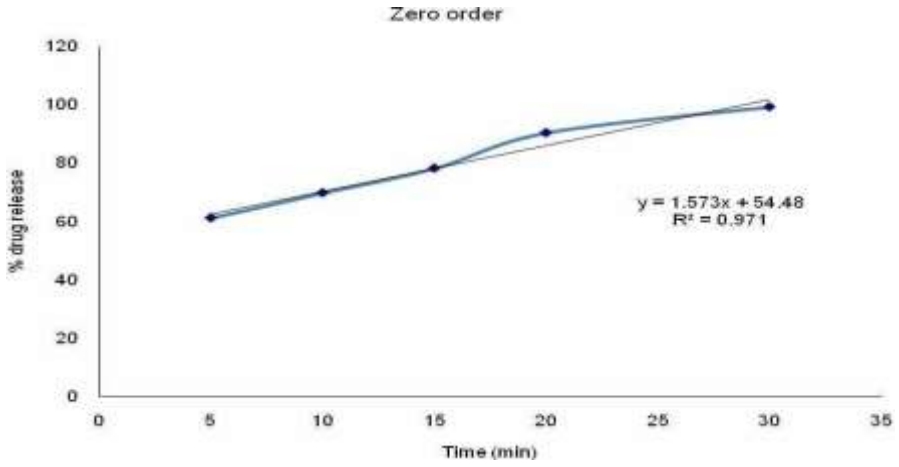

Fig. 2 Graph for the Formulation F3-Zero Order Kinetics

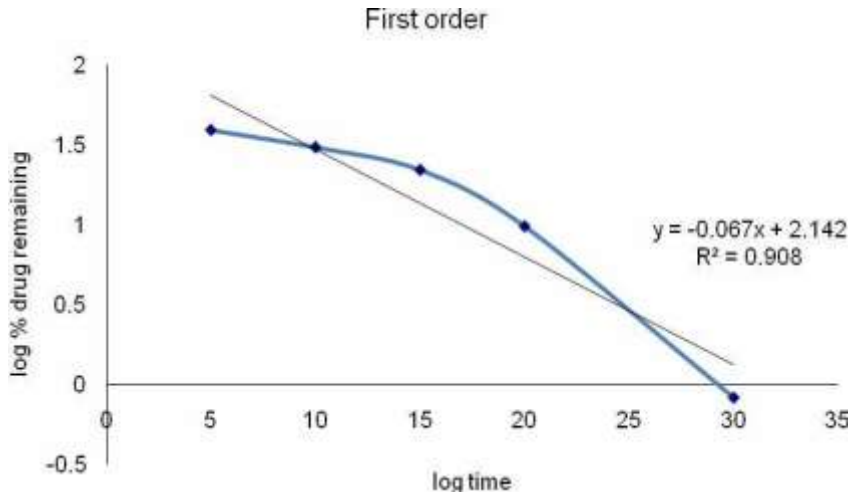

Fig. 3: Graph for the Formulation F3-first Order Kinetics

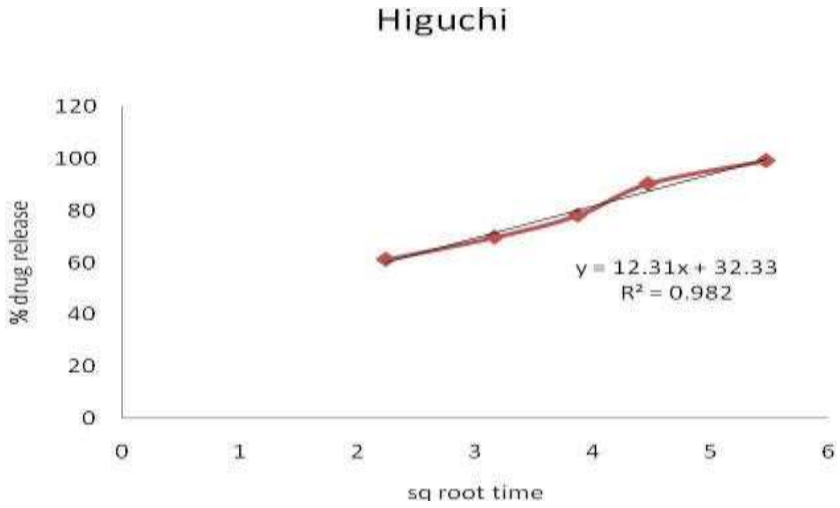

Fig. 4: Graph for the Formulation F3-higuchi model

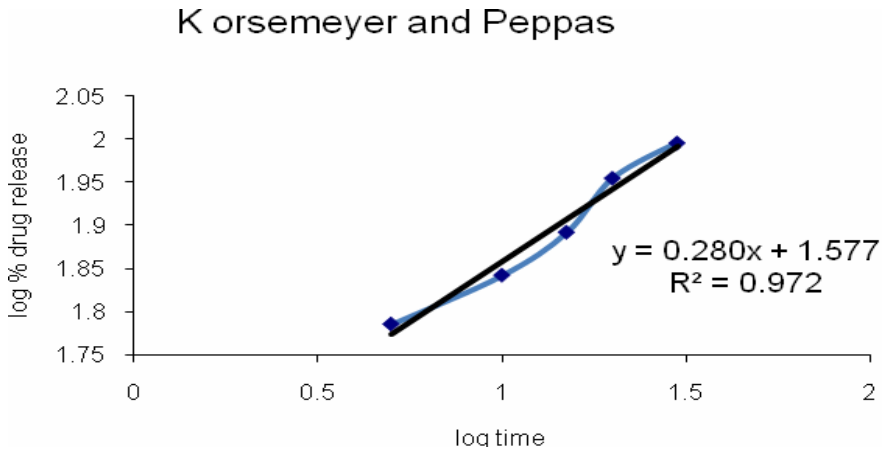

Fig. 5: Graph for the Formulation F3-Korsmeyer-Peppas model

Table 6: Stability Studies for F3 Formulation of Tramadol Hydrochloride ODT at 40º C /75 % RH

Batch number and stability condition	**Assay (%)**	**Dissolution study in pH 1.2 buffer**
40º C/75 % RH (Initial)	99.12%	99.18±0.16%
40º C/75 % RH (15 days)	99.64%	99.14±0.32%
40º C/75 % RH (1 month)	99.64%	99.76±0.12%

All values are expressed as mean ± SD, n=3

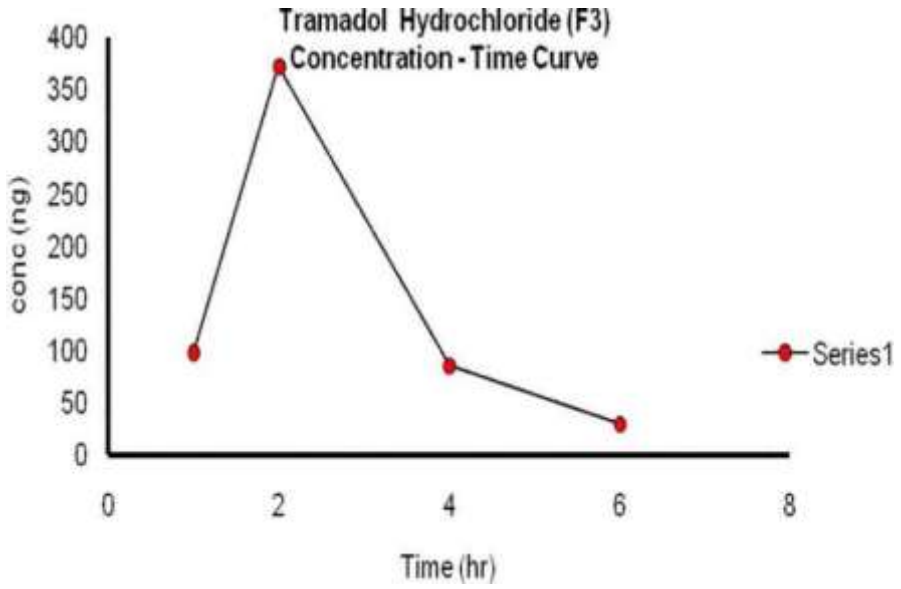

Fig. 6: *invivo* Pharmacokinetic Parameters for Tramadol hcl(F3)

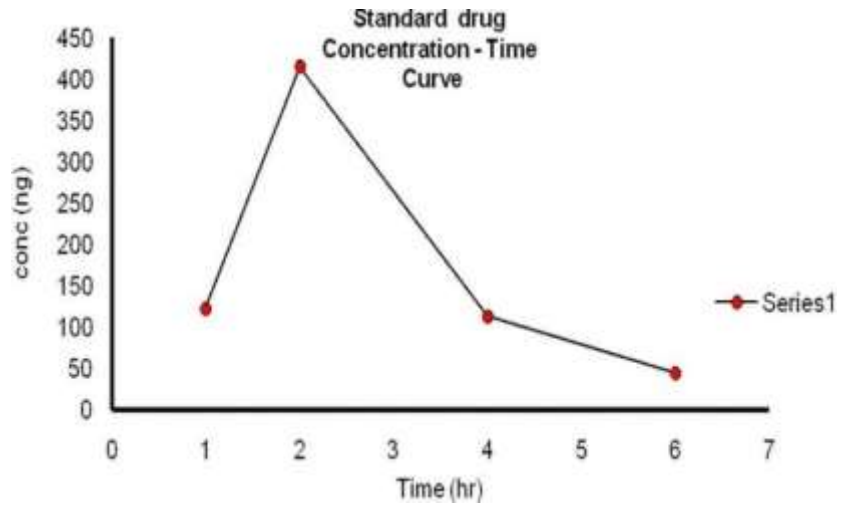

Fig. 7: *invivo* Pharmacokinetic Parameters for Tramadol hcl(A) and Marketed Product(B)

Table 7: Pharmacokinetic Parameters of Tramadol Hcl and Marketed Product

Parameters	**Tramadol Hcl**	**Marketed formulation**
Cmax	371.5	414.6
Tmax	2.0	2.0
AUC(0-t)	857.5 ng-hr/ml	1014.2 ng-hr/ml
AUC(∞)	915.2 ng-hr/ml	1110.8 ng-hr/ml
AUMC(∞)	2536.8 ng-hr*hr/ml	3325.1 ng-hr*hr/ml
E Phase	695.112	716.463
D/A Phase	772.892	830.576
MRT (area)	2.8 hr	3.0 hr

Tramadol Oral Dispersible Tablets were prepared using different percentages of Cros povidone, Croscarmellose sodium and SSG as super disintegrants by direct-compression method. The granules prepared using Cros povidone, Croscarmellose sodium and SSG as super disintegrants for compression of orally disintegrating tablets were evaluated. the prepared granules exhibited good flow properties. The results were shown in Table 2.

On immersion in 0.1M HCl, pH 1.2 solution at 37±0.50 c all oral dispersible tablets remained buoyant up to 30 min. Cross povidone due to their non-ionic nature, pyrolidone chemistry and porous particle morphology, will rapidly absorb water via capillary action. Other super disintegrants, like sodium starch glycolate and croscarmallose sodium have lower crosslink density and as a result, form gels when fully hydrated, particularly at higher use. F3 with 4% cros povidone had better dissolution properties. Stability studies were conducted for the formulation F3. The stability study was performed at 400 C±20 C/75% RH for a specific period of time.. The overall results showed that the formulation is stable at the above mentioned storage conditions shown in Table 6. In invivo studies were done to find out the pharmacokinetic parameters of the optimized formulation with the market product.The Cmax for the innovator product was found to be 414.58ng/ml and for the Tramadol hydrochloride (F3) was found to be 371.51ng/ml. The Tmax of the innovator product and Tramadol hydrochloride (F3) shows at 2nd hour. AUC(0-t) for the innovator product and Tramadol HCl (F3) was 1014.2 ng-hr/ml & 8575.5 ng-hr/ml. AUMC) shows 33.21ng-hr*hr/ml & 2536.8 ng-hr*hr/ml for innovator product and Tramadol HCl.

6. CONCLUSION

The composition containing 50mg of Tramadol hydrochloride was prepared as an oral dispersal tablet. These methods are especially useful for geriatrics and children can be taken without the help of water.

Improved formulation has a consistent release profile to provide a one-minute breakdown with Crospovidone (F3). Short-term stability studies also show that there is no change in the physical aspect of the drug content.

Comparison of pharmacokinetic parameters between ODTs Tramadol HCl and standard tablet, did not show significant changes in pharmacokinetic parameters. Therefore, it can be concluded that Tramadol HCl ODTs have been successfully developed and tested.

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