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Formulation and Evaluation of Microparticles for Controlled Delivery of Tramadol Hydrochloride

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ABSTRACT

Although Tramadol has less analgesic power than morphine, it presents fewer side effects and consequently is currently considered as a drug of choice in the treatment of chronic pain. The aim of the present work was to study preparation of controlled drug delivery of Tramadol HCl via oral route. Drug was encapsulated within polymethacrylate copolymer i.e. Eudragit RS100 and Eudragit RL100, by solvent evaporation method using acetone/liquid paraffin system. FTIR and DSC of Tramadol HCl and it combination with Excipients shows no change in peak of absorbance and melting point. Microparticles of different drug-polymer concentrations 1:1, 1:2, 1:3 and 1:4 were prepared. Magnesium stearate was used as droplet stabilizer and lubricant in concentration of 0.3% (v/v). Selected formulations were characterized for their micromeritics property, % yield, drug loading, particle size, surface morphology and release behaviour. *In-vitro* dissolution tests were performed by using dissolution media with two different pH i.e. 1.2 pH for 2 hrs and 6.8 pH for 10 hrs. All the selected formulations exhibited a controlled release for almost 12 hrs. Among the entire prepared batches F25 shows good % drug loading (48.33%), high % yield (93%) and good controlled release (98%) within 12 hrs. The mean particle size of microspheres ranged from 252 ± 24.54 µm. Scanning electron microscopy of microspheres revealed a spherical and uniform appearance with smooth surface. Stability study was performed for batch F10 shows 96.78% drug release in 12 hrs. Release of TmH was best fitted to Higuchi model and Korsmeyer-Peppas model because it presented highest values of correlation coefficient (R^2 = 0.9822).

KEYWORDS

Tramadol HCl, Microparticles, Eudragit RS100 and RL100, Scanning Electron Microscopy.

INTRODUCTION

Controlled drug-delivery technology represents one of the frontier areas of science, which involves multidisciplinary scientific approach, contributing to human health care. It is the most striking and challenging area in medical sciences, chemistry, materials science, pharmaceutics, and other biological sciences.[1]

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Microparticles are one of the key novel drug delivery systems has been widely used to precisely modulate release-rate. Microparticles based polymeric systems fabricated using suitable carrier have been extensively explored as an effective matrix for controlled and sustained release delivery of many drugs over past decade. Controlled drug release methods such as biodegradable polymer microencapsulation are technique used for increasing the duration of action and decreasing the toxicity of drug. With the controlled release systems, the rate of drug release matches the rate of drug elimination, and therefore the drug

concentration is within the therapeutic window for the vast majority of the 24-hr period.[2]

Tramadol Hydrochloride is an opioid agonist, centrally-acting analgesic indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. It is administered when NSAIDs, acetaminophen, or COX-2 inhibitors alone fails to relieve pain. Tramadol hydrochloride has very short half life about 25 minutes. It also achieves peak plasma concentration within 3 hrs and it eliminates in about 6 hrs.[3]

Eudragit polymers are series of acrylate and methacrylate polymers available in different ionic forms. Eudragit RL and Eudragit RS are insoluble in aqueous media but they are permeable and both have pH-independent release profiles. Eudragit RS100 and Eudragit RL100 are referred to as aminomethacrylate copolymers with the former having 5% functional quaternary ammonium groups and later having 10% functional quaternary ammonium groups which are responsible for permeability of water in polymer matrix.[4]

The aim of this study was to prepare Eudragit microspheres containing Tramadol HCl by solvent evaporation method to achieve a controlled drug release profile. Investigation of the effect of various processing and formulation factors such as polymer type, drug: polymer ratio, stirring speed to obtain spherical particles. Then yield of production, shape, and mean particle size, particle size distribution, encapsulation efficiency, surface properties and release rate of drug from the microspheres were performed.

MATERIALS AND METHODS

MATERIALS

Tramadol HCl was obtained from Piramal Healthcare, Eudragit RS100 and Eudragit RL100 was procured from Evonik Degussa. Magnesium Stearate, Acetone, Methanol, Liquid paraffin and n-Hexane was purchased from S. D. Fine Chemicals.

DRUG AND EXCIPIENT COMPATIBILITY STUDY

Drug - Excipients Compatibility Study by FT-IR[5]

Fourier-transform infrared **(**FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The Compatibility of Tramadol with Eudragit RS100, Eudragit RL100, magnesium stearate individually and combine in physical mixture were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample:KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}

Drug - Excipients Compatibility Study by DSC[6]

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The samples were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.

PREPARATION OF MICROPARTICLES[7]

Microparticles of Tramadol HCl were prepared by Eudragit as polymer by single emulsion solvent evaporation technique. Polymer and drug (Tramadol HCl) were dissolved in 15ml mixture of acetone and methanol. 100 mg of magnesium stearate was added to it as dispersive agent that helps to prevent aggregation between particles. The polymeric solution was then poured to 100 ml of light liquid paraffin and n-Hexane in a ratio of (8:2). The solution was stirred for 3 hrs at 800 rpm to evaporate the solvent. Microparticles were collected by vacuum filtration and washed with petroleum ether 2-3 times and dried at room temperature for 24 hrs.

Table 1: Composition of Tramadol Microparticles

Batch code	Ratio (drug: polymer)	Polymer used (Eudragit grade)	Eudragit ratio
F1	1:2	RS100	--
F2	1:2	RL100	--
F3	1:2	RS100:RL100	1:1
F4	1:3	RS100	--
F5	1:3	RL100	--
F6	1:3	RS100:RL100	1:1
F7	1:4	RS100	--
F8	1:4	RS100:RL100	1:1
F9	1:3	RS100:RL100	8:2
F10	1:3	RS100:RL100	7:3
F11	1:3	RS100:RL100	6:4

EVALUATION OF MICROPARTICLES[8]

Percentage Yield

Microparticles after drying at 40°C were weighed to calculate the percentage yield of microparticles using the following formula:

$$\% \text{ yield} = \frac{\text{Total amount of microparticles}}{\text{total weight of drug and polymer}} \times 100$$

Drug Loading

100 mg of microparticles were accurately weighed and crushed in mortar pestle. Crushed particles were soaking in 100 ml of distilled water. Solution was then sonicated and stirred for 24 hrs. The solution was then filtered and filtrate was appropriately diluted and measured the absorbance in UV Visible spectrophotometer at λmax 271nm.

Bulk Density and Tapped Density

The microspheres fabricated are weighed and transferred to a 10-ml graduated glass cylinder. The volume was measured which are known as bulk volume. The cylinder is tapped until the microsphere bed volume was stabilised and tapped volume was measured. Bulk and tapped density was calculated from bulk and tapped volume.

Angle of repose

The maximum angle which is formed between the surface of a pile of powder and horizontal surface is called the angle of repose.

Particle size analysis[9]

Particle size distribution of the microspheres was determined by optical microscopy using calibrated ocular eyepiece. Product dispersed in light liquid paraffin and a smear of the dispersion was observed under compound microscope. The size of 50 microparticles was measured in each case against a calibrated eyepiece in micrometer.

In-vitro drug release study[10]

Microparticles were evaluated for *in-vitro* release study in simulated gastric fluid and phosphate buffer 6.8 pH. The drug dissolution test of microspheres was carried out using USP rotating paddle method. 100 mg equivalent to Tramadol HCl microparticles was placed in basket. The content was rotated at 100 rpm at 37 ± 0.5ºC. 5 ml of sample was collected at each hour to measure UV absorbance and replaced with 5 ml of fresh media. First 2 hrs of dissolution was performed in 0.1 M HCl. After 2 hrs, dissolution was carried out in phosphate buffer 6.8 pH and also replaced with same media. The sample aliquots were collected up to 12 hrs. The absorbance of sample was then measured in UV Visible spectrophotometer at 271 nm.

Scanning Electron Microscopic Analysis[11]

The shape and surface morphology of Tramadol HCl microparticles were investigated using scanning electron microscopy. The samples for

SEM study were prepared by lightly sprinkling the formulation on a double-adhesive tape stuck to an aluminum stub. The samples were then randomly scanned at 15 accelerated voltage and different magnification of 35 and 100 times were taken with a scanning electron microscope (Jeol JSM-5610, Tokyo, Japan).

APPLICATION OF KINETIC MODELS[12, 13]

The dissolution data of all controlled-release microparticles and control formulation was fitted to kinetics models i.e., zero order, first order, Higuchi, Korsmeyer–Peppas and Hixson Crowell to find out drug release pattern and mechanism.

STABILITY STUDY OF OPTIMIZED BATCH[14]

Stability studies were performed according to ICH and WHO guidelines. Batch F25 was packed in an airtight amber glass bottles. The bottles were kept at 25ºC ± 2ºC / 60% RH ± 5% RH and 40ºC ± 2ºC / 75% RH ± 5% RH tested at 1 month. The sample of microparticles was than evaluated for stability by determining drug content and physical appearance.

RESULT & DISCUSSION

Drug - Excipients Compatibility Study by FT-IR

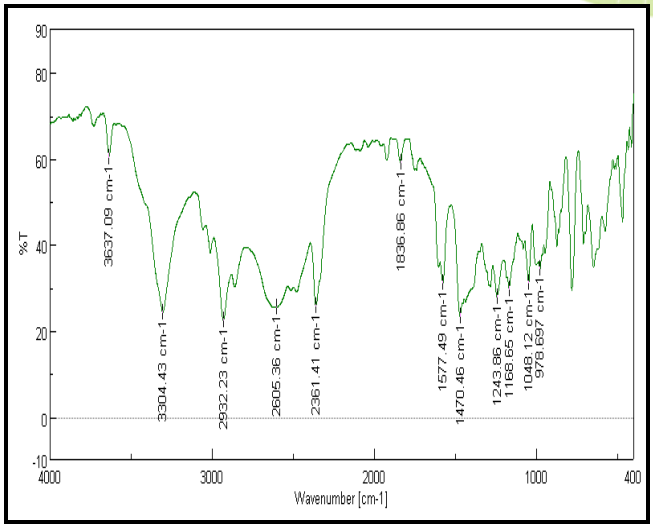

Figure 1: FT-IR Spectra of Tramadol HCl

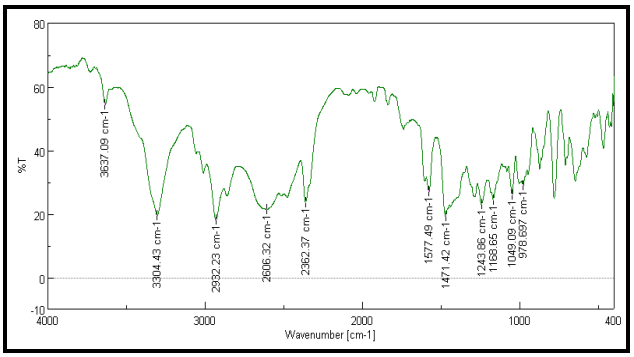

Figure 2: FT-IR Spectra of Tramadol HCl and Eudragit RS100

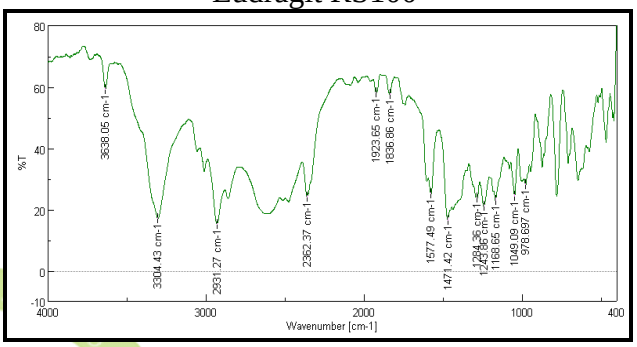

Figure 3: FT-IR Spectra of Tramadol HCl and Eudragit RL100

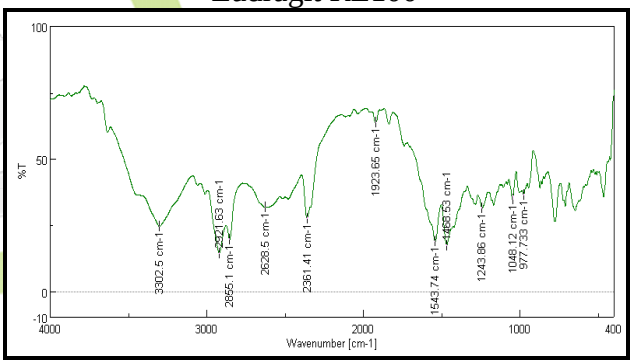

Figure 4: FT-IR Spectra of Tramadol HCl and Magnesium Stearate

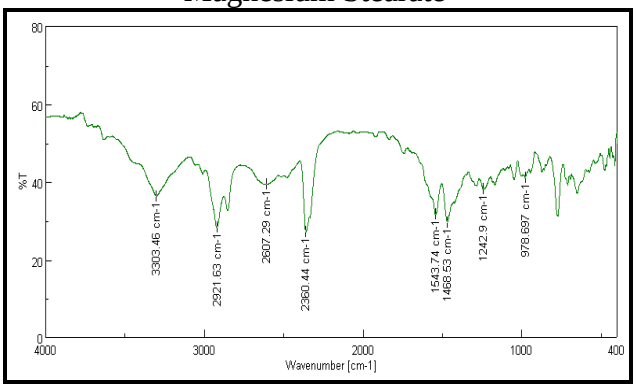

Figure 5: FT-IR Spectra of Tramadol and all Excipients

In the FTIR spectrum of TmH, the characteristics of aromatic CH stretching vibration about 3052.48 cm^{-1}, OH shoulders about 3637.09 cm^{-1}, aliphatic CH stretching vibration about 2932.23 cm^{-1}, and aromatic ring stretching vibration about 1577.49 cm^{-1} are observed. It was clear that from above IR peaks obtained for different function groups of Tramadol HCl present in microspheres were not much deviated from peak obtained in standard Tramadol HCl. Therefore, it was concluded that different materials were used in preparation of Tramadol HCl microspheres were compatible with Tramadol HCl[15].

Drug – Excipients Compatibility Study by DSC

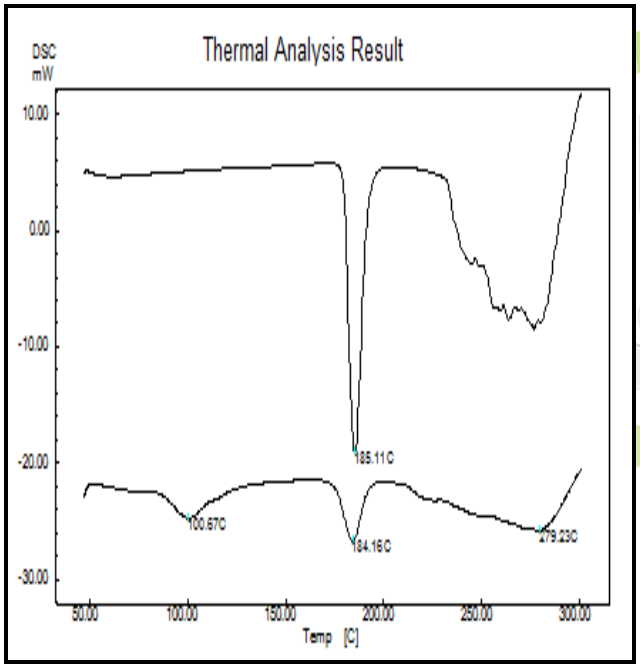

Figure 6: DSC of Tramadol HCl and with formulation mixtures comparison

The DSC thermogram of the Tramadol HCl and mixture with other ingredients shows endothermic peak at 185.11°C and 184.16 °C respectively. There is no change in the melting endotherm of the drug and excipient mixture. So, it was concluded that drug and Excipients are compatible with the each other.

Bulk Density and Angle of Repose

Table 2: Flow Property of Microparticles

Batch No.	Bulk Density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Angle of Repose
F1	0.47 ± 0.01	0.57 ± 0.05	1.21 ± 0.03	25.36 ± 1.53
F2	0.45 ± 0.04	0.52 ± 0.01	1.15 ± 0.05	24.12 ± 1.49
F3	0.46 ± 0.03	0.50 ± 0.03	1.08 ± 0.06	26.38 ± 1.87
F4	0.44 ± 0.06	0.53 ± 0.06	1.20 ± 0.02	22.87 ± 2.24
F5	0.48 ± 0.02	0.59 ± 0.04	1.22 ± 0.03	25.49 ± 2.18
F6	0.39 ± 0.06	0.51 ± 0.02	1.30 ± 0.01	23.83 ± 1.97
F7	0.37 ± 0.01	0.53 ± 0.03	1.43 ± 0.04	24.76 ± 1.85
F8	0.41 ± 0.01	0.51 ± 0.05	1.24 ± 0.02	26.59 ± 2.05
F9	0.46 ± 0.03	0.56 ± 0.04	1.21 ± 0.03	24.60 ± 1.65
F10	0.46 ± 0.05	0.55 ± 0.01	1.19 ± 0.05	23.31 ± 1.89
F11	0.43 ± 0.03	0.56 ± 0.02	1.30 ± 0.02	23.92± 2.09

*All the reading were calculated as mean value and with standard deviation where n=3.

Angle of repose of microparticles was found in the range of 22- 29º which indicates good flow property. The pure drug was fluffier, which was indicated by the lowest loose bulk density value.

The high tapped density value of pure drug indicates a high inter-space between drug crystals. In contrast, the microparticles exhibited higher loose bulk density than pure dug. It also has low tapped density of microparticles which indicates low inter space between particles.

Percentage Yield and Percentage Drug Loading

Table 3: % Yield and % Drug Loading

Batch code	% Yield	% Drug Loading
F1	76.87	43.35
F2	78.75	42.73
F3	83.75	44.85
F4	84.28	50.4
F5	79.04	54.18
F6	70.00	43.18
F7	85.00	48.48
F8	80.00	39.49
F9	85.23	42.09
F10	93.00	48.33
F11	87.50	43.47

*All the reading were calculated as mean value and with standard deviation where n=3

By increasing in polymer concentration ratio with drug, it increases the % drug loading. Highest % drug loading as shown in table 4 was found in batch F4 and F5 which are having drug: polymer ratio 1:3. Eudragit RS100 and Eudragit RL100 were used in the batch F4 and F5. To increase the % yield and % drug loading, different batches were prepared using combination of both the grades of Eudragit. Batch F9, F10 and F11 were prepared by combination of Eudragit RS100 and RL100 with ratio of 8:2, 7:3 and 6:4 respectively.

Particle Size Analysis

Particle size analysis was performed by optical microscopy of microparticles. Microparticles show spherical in shape as shown in figure 7.

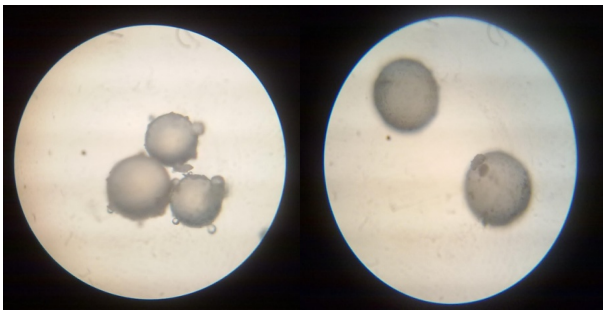

Figure 7: Microphotographs of Microparticles Batch F10

The particles size of batch F10 shown in above photograph was found to be in range of 250 to 480 µm. Particle size of all the prepared batches were given in the table 4.

Table 4: Particle Size of Batch F1 to F11

Batch Code	Mean Particle Size (µm) ± SD
F1	256 ± 28.42
F2	242 ± 26.85
F3	237 ± 16.16
F4	371 ± 24.73
F5	335 ± 20.62
F6	326 ± 22.48
F7	365 ± 32.28
F8	374 ± 27.94
F9	343 ± 19.17
F10	360 ± 24.54
F11	363 ± 27.07

*All the reading were calculated as mean value and with standard deviation where n=50

In-Vitro Drug Release Study

In-vitro drug release study was performed using USP apparatus II in 0.1 N HCl for first two hrs and then in phosphate buffer 6.8 pH for other 10 hrs and the graphs was plotted between Time Vs % Cumulative Drug Release. % Cumulative Drug Release from batch F1 to F11 was shown in figure 8 to 11.

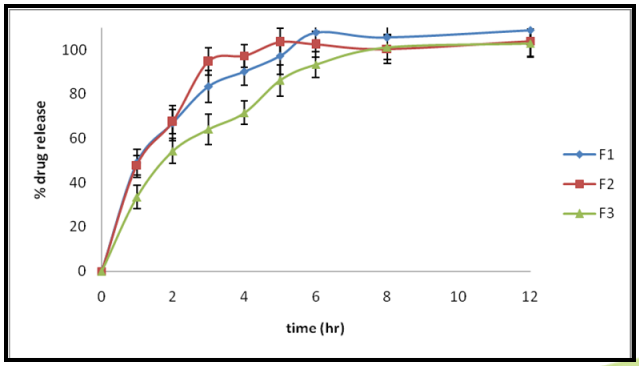

Figure 8: Comparative Study of Batch F1, F2 and F3

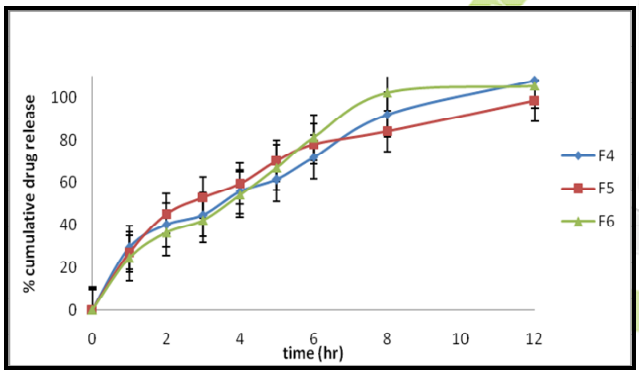

Figure 9: Comparative Study of Batch F4, F5 and F6

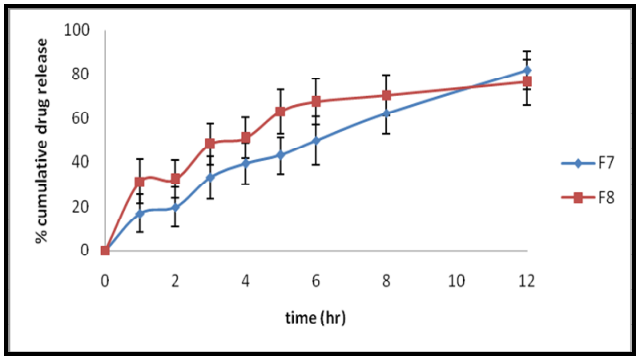

Figure 10: Comparative Study of Batch F7 and F8

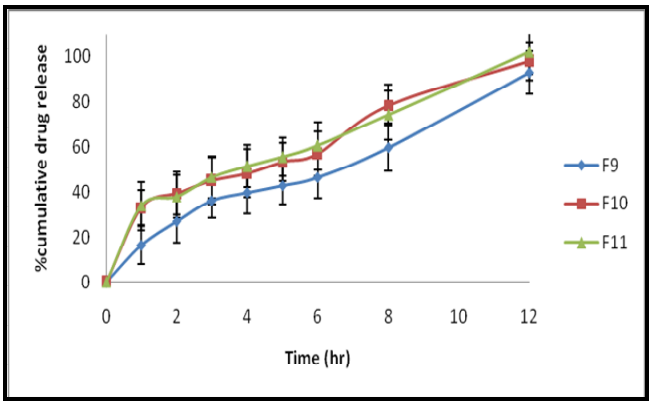

Figure 11: Comparative Study of Batch F9, F10 and F11

From the graphs of *in-vitro* drug release study, it was observed that batch F1, F2 and F3 containing drug: polymer ratio 1:2 has shown drug release within 6 hrs. Batch F4, F5 and F6 containing drug polymer ratio 1:3 shown better drug release compare to previous three batches. Batch F7 and F8 have a drug polymer ratio of 1:4, and so it was observed that drug release can be controlled for more than 12 hrs. So, further batches F9, F10 and F11 were developed using 1:3 drug-polymer ratio but having different proportion of Eudragit RS100 & Eudragit RL100 i.e. 8:2, 7:3 & 6:4 respectively. All the three batches have good drug loading capacity and also show controlled drug release upto 12 hrs. But batch 10 has shown 48.33% drug loading and 97% drug release at 12 hrs compared to other batches F9 and F11.

Scanning Electron Microscopic Analysis

Surface morphology study was performed by Scanning Electron Microscope (SEM) for final formulation of Tramadol HCl microparticles.

Microparticles were observed at 35 and 100 times magnification and at 15 kV in JSM-5610. SEM of final formulation i.e. drug: polymer ratio of 1:3 and polymer-polymer ratio of 7:3 microparticles shows particles in spherical shape. The smooth and even surface was because of highly plasticizing nature of Eudragit.

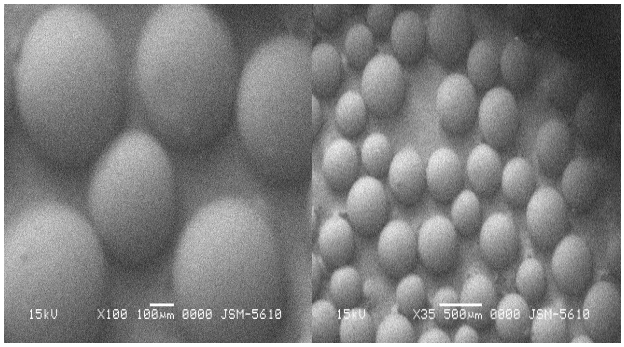

Figure 12: SEM of Batch F10

APPLICATION OF KINETIC MODEL

The release kinetic of the formulation was checked by fitting the release data to various kinetic models. The release was best fitted to the Higuchi model. It was further confirmed by fitting the data to Korsmeyer-Peppas equation and the value for all the formulation obtained between 0.530-0.733. It was revealed that the release was followed square root of time mechanism. The R^2 values for all the models are shown in table 5.

STABILITY STUDY OF OPTIMIZED BATCH F10

The selected formulation F10 were evaluated for stability studies which were stored at 25ºC ± 2ºC / 60% RH ± 5% RH and 40ºC ± 2ºC / 75% RH ± 5% RH tested for 1 month, and were analyzed for their Physical appearance, drug content and *in-vitro* drug release at that interval. The residual drug contents of formulations were found to be within the permissible limits and the results of 1 month's duration are shown in the table 6. *In-vitro* release study was performed for batch F10 and it was found to within permissible limit for both stated condition.

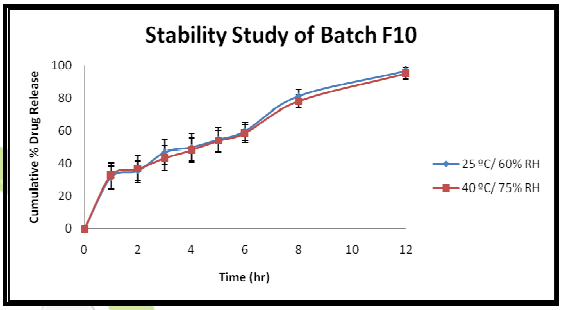

Figure 13: Stability Study of Batch F10

Table 5: Different Kinetic Models Applied on Final Batches of Microparticles

Batch code	Zero order			First order			Higuchi square root model			Korsmeyer-Peppas Model				Hixson-Crowell Model		
	K_0	SSQ	R^2	K_1	SSQ	R^2	K_H	SSQ	R^2	N	K_{KP}	SSQ	R^2	K_{HC}	SSQ	R^2
F9	8.12	440.12	0.9832	0.131	349.40	0.9687	21.935	441.80	0.9685	0.733	14.153	140.50	0.9876	0.038	292.77	0.9752
F10	9.53	1651.34	0.9554	0.186	579.98	0.9576	26.418	214.79	0.9822	0.530	24.994	206.85	0.9832	0.052	649.08	0.9611
F11	9.73	1669.40	0.9589	0.193	576.78	0.9589	26.972	183.05	0.9854	0.531	25.472	174.23	0.9864	0.053	650.81	0.9618

R^2-Correlation coefficients, K_0, K_1, K_H, K_{KP}, K_{HC} Release rate constant for zero order, First order, Higuchi, Korsmeyer- Peppas and Hixson Crowell release equation, respectively, n, diffusional exponent, indicative of release mechanism in Korsmeyer equation.

Table 6: Stability Study of Optimized Batch F10

Time	Initial drug content of batch F10	Batch F10 stored at 25ºC ± 2ºC / 60% RH ± 5% RH			Batch F10 stored at 40ºC ± 2ºC / 75% RH ± 5% RH		
		Physical appearance*	%Drug content	% Drug Release	Physical appearance*	%Drug content	% Drug Release
1 month	48.33%	+++	47.94%	96.78%	+++	47.78%	95.16%

***+++ = Same as on zero day**

CONCLUSION

Tramadol HCl microparticles were prepared successfully using solvent evaporation method. Drug and polymers were compatible with each other as indicated by FT-IR and DSC. The yields of preparation and % drug loading were enough for all microparticles obtained. It was concluded that addition of magnesium stearate in the formulation gives free flow property of microparticles. Tramadol HCl release rates from microparticles were dependent on the type of polymer used. Tramadol HCl release rates from Eudragit RS microparticles were very slow whereas release rates from Eudragit RL microparticles were faster. Combination of both the polymer gives good controlled release of TmH microparticles. Among the different formulations prepared in this study, batch F10 has shown batch 10 has shown 48.33% drug loading and 97% drug release at 12 hrs. Higuchi model and Korsmeyer-Peppas model was found to be the best model.

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