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Research Article

EFFECT OF POLYMERIC BLEND ON THE DISSOLUTION BEHAVIOR OF SPRAY-DRIED MICROPARTICLES

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ABSTRACT

The purpose of present study was to investigate the effect of hydrophilic and hydrophobic polymeric blend on sustained release of Tramadol-Hydrochloride (T-HCL) microspheres prepared by spray-drying. Different polymeric concentrations were used as feed solutions by varying the polymer to polymer ratio. Specific spray-drying conditions were used by optimizing process parameters. The spray-dried microspheres were characterized in terms of size distribution, morphology, interaction using FTIR, DSC study, polymorphic behaviour using XRD study and also evaluated by means of production yield, drug content, initial drug loding, encapsulation efficiency, in-vitro drug release and release kinetics. Drug encapsulation efficiency was ranging from 65.50-94.30%w/w, the results indicated that the entrapment efficiency and product yield were depended on polymeric composition and polymer: polymer ratios of the microspheres prepared. Scanning electron microscopy revealed particle size of microsphere was between 13.375-20.59 µm. FTIR spectra and DSC thermograms demonstrated no interaction between drug and polymer. XRD pattern indicating amorphous nature of drug after encapsulation into the polymeric microspheres. Based on the results of Laser diffraction particle size analyzer; comparatively narrow size distribution was obtained, it may be because of lower viscosity of the spray solution, aspirator speed and feed pump flow rate. The combination of both the polymeric solution approach helps to achieve desired sustained release effect upto 12h. In-vitro release data showed correlation (r2> 0.985), good fit with Higuchi/ Korsmeyer-Peppas models, exhibited non Fickian diffusion. The best fit of release model was Baker-Lonsdale that describes the release rate of drug from a spherical matrix.

Keywords: Tramadol-Hydrochloride, HPMC, Eudragit-RS100, Microspheres, Spray-drying

INTRODUCTION

A sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for an extended period of time with minimized local or systemic adverse effects give better economy and greater patient compliance[1]. Microspheres are one of the key novel drug delivery systems Are been widely used to precisely modulate release-rate. Microsphere 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. In recent years, clinical studies on Tramadol hydrochloride (T-HCL) is a synthetic centrally acting aminocyclohexal analgesic that acts as

an opioid agonist with selectivity for the μ receptor have demonstrated that this drug is an effective agent for moderate to severe chronic pain[2-3]. The half life of the drug is about 5.5 h and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 h with a maximum dosage of 400 mg/day. To reduce frequent administration of dosage form and to improve patient compliance, a sustained-release formulation of tramadol is desirable. The drug is freely water soluble and hence judicious selection of release retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug[4]. Frequent dosing schedule often leads to decreased patient compliance, increased incidence of side effects and tolerance development, especially, in long-term use in conditions like arthritis, osteoarthritis, arthralgia, postoperative surgical pains, *etc*. It seems that there is a strong clinical need and market potential for a delivery system that can deliver T-HCL in a controlled manner[5-8].

Cellulose ethers, especially hydroxylpropyl methylcellulose (HPMC) is often used to prepare the matrix type sustained release formulation. Their properties as gelling agents are very important in the formulation because they are responsible for the formation, by hydration, of a diffusion and erosion-resistant gel layer which is able to control drug release[9]. On the other hand, hydrophobic materials have also been employed as matrix carriers for sustained release solid dosage forms. EudragitRS100 is a non-toxic, stable, biocompatible, compressible, inert, hydrophobic polymer having properties for sustained release products. The combination of Methacrylate polymer and a hydrophilic component such as HPMC offers a flexible system to tailor the drug release by changing the viscosity, substitution type and concentration of HPMC[10].

The success of the spray-drying process is related to the degree of core material encapsulation, as well as to the physicochemical characteristics of the spray-dried microparticles, which both depend upon factors such as the type of feed (i.e. active material in solution or dispersed as solid particles in the polymer solution) and the polymer/polymer ratio[11-13]. The properties of spray-dried powders are controlled by both the process and formulation parameters such as inlet and outlet temperatures, spray rate of feed, exhausting concentration, and drug–polymer ratio of the polymeric feed solution[14].The purpose of the present study was to investigate the effect of polymeric-blend of on sustained release dissolution rate of T-HCL.

MATERIALS AND METHODS

MATERIALS

Tramadol-HCL acquired as a gift sample from COMED Pharmaceuticals Ltd. (Baroda, Gujarat, India). Eudragit RS-100 granules were gifted from Evonik Pharma Pvt. Ltd, (Mumbai, India). HPMC is a kind gift from Colorcon Pvt. Ltd, (Mumbai, India) All ingredients, solvents and reagents were of analytical grade.

METHODS

Formulation of sustained release Microsphere

Microsphere Preparation

Matrix–type microspheres of Tramadol-HCL containing hydrophilic-hydrophobic polymeric blend were produced using a laboratory spray-dryer, model-LU222 (Labultima Advanced, Mumbai), a co-current spray dryer apparatus equipped with the high-performance cyclone.

On the basis of literature data and of preliminary experiments carried out, formulations were prepared using different proportions of HPMC K-15M, dissolved in a 100ml warm water to obtain specific concentration as shown in **Table-1** under constant stirring at 500-800 rpm for 4 hour , then pure drug was dissolve into it till complete homogenous solution obtained. Different proportions of Eudragit-RS100 were dissolve in 50ml Ethanol under continuous stirring at 200 rpm on magnetic stirrer for 2hr. Then mix both the polymeric solution (Blend) at different ratio of 1:1,1:2,2:1,1:3,3:1 (ratio of polymer: polymer).

The solution was fed into the instrument by a peristaltic pump, set up at 10% of its capacity, at the feed pump rate of 5ml/min, and sprayed through the 0.5mm nozzel, by 200 l/h compressed air flow. A flow of heated air at 75^0C, aspirated by 45% of aspirator capacity, induced the quick evaporation of the solid particles in the cyclone from where they were collected. All the formulation obtained and the respective spray-drying conditions used were

listed in Table 2. These formulations were produced three times for verifying the method reproducibility. Four different formulations (M1-M4) were produced by decreasing the peristaltic pump capacity. The inlet temperature was set at 70-75 °C for M1-M4 formulation, while it was reduced from 90°C to 50°C for preparing the M6 and M7 formulation respectively.

Microsphere Characterization

Particle size analysis

A optical microscopical image analysis technique would be applied for determination of particle size. Particle size distribution were determined using laser diffraction particle size analyzer (SALD-2101 Shimadzu, SICART) by wet method using water as dispersant. The sample was vortexed at 50 rpm stirring speed, sonicated in a sonicator attached to the instrument throughout the process. The microparticle size distribution is expressed as SPAN Index (SI) calculated applying the following equation:

$$SI = \frac{d_{90} - d_{10}}{d_{50}} \quad \text{..... (1)}$$

where d_{10}, d_{50}, d_{90} indicate the volume percentage of particles (10,50,90%respectively) having a mean diameter lower than the obtained value.

Morphological Analysis

The surface morphology & surface characteristics of samples were studied by scanning electron microscopy (SEM). The powder sample was sprinkled onto the tape. The aluminum stubs would be placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, SICART). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 kV) XL 30, Philips (Eindhoven, The Netherlands).

Infrared (IR) spectroscopy

IR spectroscopy would be conducted using a FTIR Spectrophotometer (Spectrum GX-FT-IR, Perkin Elmer, USA) for pure drug, pure excipients and drug loded microparticles. The spectrum was recorded using (0.02% w/w in potassium bromide) in the wavelength region of 4000–400 cm^{-} and resolution of 0.15 cm^{-1}at scan speed 20scan/sec.

Differential scanning calorimetry (DSC)

DSC would be performed using Differential Scanning calorimeter (DSC-PYRIS-1, Phillips, SICART) to study the thermal behavior of drug and drug loded microparticles. The samples were heated in hermetically sealed aluminium pans and a scanning rate of 10 C/min from 50±0.2˚C - 550±0.2˚C and calorimeter measuring range was 1µW to 750mW.

X-ray diffraction (XRD)

The X-ray diffraction study would be carried out to characterize the crystalline or amorphous form of Tramadol-HCL in samples of selected batch. The samples were analyzed by spread on the glass slide in approximately 0.5 mm thickness. The slide was then placed vertically at 0° angle in the X-ray diffractometer (X"Pert Model, Phillips, SICART) so that the X-ray beam fell on it properly. The results were recorded over a range of 0–90^0(2θ) using the Cu-target X-ray tube and Xe-filled detector at voltage 40 kV; current 20 mA; scanning speed 1/min.

Evaluation of Microsphere

Determination of drug loading and Entrapment-efficiency

The total amount of Tramadol-HCL present in the mirospheres was determined by extracting into ethanol solvent. The weighed amount of microspheres was dissolved in 10ml Ethanol by continuous stirring for period of 2hr. and then kept aside for 24hr. The drug content was measured spectrophotometrically at 271 nm using UV-visible spectrophotometer (Shimadzu). The total amount of Tramadol - HCL was calculated by using regression equation of the calibration curve.

In-vitro drug release study of Microsphere

Dissolution rate studies were performed using USP dissolution Type II rotating paddle apparatus (Electrolab, TDT-06T, Mumbai, India) in 900 ml Deionized doubled distilled water at 37 ± 0.5^{0}C at 50 rpm for 12 h. Microsphere equivalent to 100mg of drug were used for test. Each 5ml of test sample was withdrawn at regular time interval of every 30min. till 2h, then every 60 min till 8 h,

then every 2h till 12h. and was replaced with fresh quantity of dissolution fluid. The samples were filtered, and then filtrate was assayed spectrophotometrically at 271 nm to determine the dissolved drug concentration. The dissolution data was treated using different mathematical equation to characterize the mechanism and kinetics of drug release.

Kinetics of drug Release

Various kinetics models were applied to analyze the in vitro release data and thereby to describe the release kinetics. The zero order rates describe the systems where the drug release rate is independent of its concentration. The first order explains the release from system where release rate is concentration dependent. Higuchi indicates the release of drug from insoluble matrix as a square root of time dependent process based on Fickian diffusion. Hixson–Crowell indicates the dissolution process from any matrix as a cubic root of time dependent process, The Korsmeyer–Peppas model explains a simple relationship which described drug release mechanism from polymer matrix, and The Baker-Lonsdale Model describe the drug controlled release from a spherical matrix.

Statistical Analysis

All the reported determinations were performed in triplicate to produce the reproducibility in result. One-way analysis of variance (ANOVA) followed by Tukey's multiple range test was performed to determine the least significance difference for all the reported evaluations. The differences were considered as significant at $p<0.05$.

RESULTS AND DISCUSSIONS

Preparation and Characterization of microspheres

The spray drying technique was found appropriate for preparing microparticle from hydrophilic-hydrophobic polymeric mixed solvent system. In ethanol-water mixture, the drug was better microencapsulated by continous stirring that give better coating of polymeric layer onto the drug. Specific stirring speed would be optimized for specific duration for better microencapsulation.

Effect of stirring speed

It was observed that when the speed of stirrer was below 500 rpm for hydrophilic solution, there was no formation of spherical microsphere. This could be due to inadequate dispersion of the inner phase of polymeric solution to the drug. At higher speed of 800rpm, the resulting high turbulence, caused frothing and adhesion to the container wall. Mixed solvent system containing both hydrophilic-hydrophobic polymeric blend was maintained at optimized condition.

Effect of spray-drying parameter

The spray-dryindg parameters like feed rate, atomizing pressure, air flow rate, and inlet temperature were optimized, because the mean size of the spray solution was affected by the gas-liquid relative velocity of the air flow from nozzel, and the feed rate had little impact on the powder properties, feed pump rate is small gives smaller the particle size and greater the product yield. It is likely that the high temperature is associated with a faster drying, which makes the surface of liquid droplet harden and the residual moisture expand, leading to the formation of hollow fluffy particles. The spray-dried product characteristics are principally affected by properties and composition of the spray-drying solution. The spray-dried microspheres appeared as free-flowing, fluffy, spherical, white amorphous powder.

Microparticle size analysis

Microscopical examination shows that the obtained microspheres were spherical with smooth surfaces (Figure-1). It shown that prepared formulation were well-round spheres with ridges of shrinkage due to presence of HPMC polymer. These microspheres had no hole or rupture on the surface such morphology would result in slow clearance and good property. Size distribution of formulation is highly dependent on variables related to the particles themselves, the method of sampling and the technique of analysis, and the way in which the data are expressed. The data of the particle size distribution of the optimized formulation was determined using High efficiency Laser differaction particle size analyzer in terms of X_{10}, X_{50}, X_{90} of the formulation and Pure drug, were reported in following Table 3.

Comparatively narrow size distribution was obtained by spray-drying process shown in figure-2; it may be because of lower viscosity of the spray solution, aspirator speed, and feed pump flow rate.

Scanning Electron Microscopy

SEM of drugs-loaded polymeric microspheres reveals that the microspheres possess rough, porous and rugged surface Fig. 3a. The surface porosity is crucial for drug release in microspheres prepared, since the polymer is not biodegradable, the release of the drugs from microspheres takes place by dissolution and diffusion through the pores. HPMC allows water to permeate through its surface without itself dissolving in it. The most part of particles was small and had spherical shape, non-uniform surface, and were coalesced. Fig. 3b.

FTIR and DSC study

FTIR spectra of pure drug and microspheres of T-HCL revealed its principle peaks of amine stretch at 1356 cm-1 and –OH stretch at 3304 cm-1 shown in Fig. 4. The IR spectrum of microsphere formulations also presented all the peaks characteristics of pure drug indicating no interaction between the drug and polymer.

The DSC thermogram of optimized formulation shown in Fig. 5 may hide the sharp peak of T-HCL. The sharp endothermic peak of T-HCL in microsphere formulation was not distinctive indicating that the the drug was no longer present in the crystalline form. The appearance of low intensity endothermic peak also indicated that the some of the drug still managed to crystallized out from the Eudragit matrices.

X-Ray diffraction study

T-HCL is crystalline, as demonstrated by sharp and intense diffraction peak at $2\theta = 17.6$. HPMC K15M is an amorphous powder having no crystalline structure. The X-ray powder diffraction patterns shown in Fig. 6 of pure drug, HPMC : Eudragit RS microspheres containing T-HCL reveals that the intensity of the peaks for the pure drug was sharp, but when it was incorporated into the polymeric matrix, the drug peaks showed a loss of sharpness due to probably decreased crystallinity of the drug. The crystalline nature of the drug was clearly demonstrated by characteristic powder XRD pattern with different appearing peak at 10.42- 29.56 2θ Theta values, but in case of formulation no intense peaks were observed between this 2θ Theta value range, indicating amorphous nature of drug after encapsulation into the polymeric matrix.

Evaluation of Microsphere

Effect of experimental variables on product Yield and particle Size measurement

The product yield and particle size of drug loded microparticles of all batches are shown in Table-4. The processing variables like polymer: polymer ratio, drug: polymer ratio, stirring rate, and also the spray-drying condition affect the particle size of the microsphere. Higher 42.55 % product yield with 17.56 µm particle size were obtained in case of 1:3 polymer blend ratio. Increasing the particle size is due to increase in viscosity, which in turn increase the droplet size during addition of the polymeric dispersion to the nozzle, also increasing the concentration of polymer slightly increased the yield. As the Eudragit conc. was increased, the product yield was increased. Alone HPMC and Eudragit polymeric solution would give 34.27% and 39.65% product yield and 19.37µm & 14.78 µm mean particle size respectively.

Determination of Drug content, Drug loading and Entrapment-efficiency of microsphere

The determination of the drug content shows good uniformity. Encapsulation-efficiency provides an assessment about the amount of actual drug content present in the micromatrix system as compared to its theoretical value. Encapsulation efficiency of drug is mainly dependent on its solubility in the solvents, physicochemical properties of drug and polymer and significantly increased as the concentration of the polymer increased.(Dubey RR; Parikh RH, 2004). In case of M1 formulation, the low value of encapsulation efficiency was probably due to the loss of drug and also the free drug present at the surface because the formation of strings during the drying process. The higher drug loading capacities might be obtained with increasing concentration of Eudragit and HPMC. (Mandal,1998). All formulations had good incorporation efficiency between 65.50-

94.30%. These results indicate very good reproducibility of the spray-drying method.

In-vitro dissolution studies

The cumulative percentage release of T-HCL from microparticels was plotted as a function of time in figure-9. All the formulations showed a release of drug in the range of 20-30% within 1hr meeting the specification of release time point recommended in USP. Formulations M6 and M7 released 90.57% drug in the 6th and 7th hour, respectively shows initial burst effect in case of formulation M6 containing HPMC alone,because hydrophilic polymer in hydrophilic solvent shows rapid release in initial time, and presence of free drug at the suface periphery of the microsphere,then it gives slow release upto 6 hour. The retardation of drug release with eudragit coating was not much as expected, So to retard the drug release from microspheres HPMC was blended with Eudragit solution to form matrix type formulation.Therefore further formulation with both HPMC and Eudragit RS100 coating yield better microencapsulation efficiency, and also better sustained release effect upto 12hour. As the concentration of Eudragit incraeases, more drug was encapsulated and higher blend composition gives better coating of drug , results in desired sustained release effect. The dissolution profile of marketed formulation follows a matrix model. The model independent method such as similarity factor (*f2)and* dissimilarity factor*(f1)* provides a simple way to compare dissolution data. USFDA guidance proposes that *f2* values of 50-100 indicate equivalence in dissolution profiles. The *f1 & f2* values for all batches were shown in Table 6. The f2 value for optimized formulation was 62.19 indicating similarity in dissolution profiles.

Release kinetics

The release of T-HCL from the polymeric microparticles under consideration may be due to diffusion phenomena or degradation effects, or a combination of both processes. The rate constants were also calculated from the slope of the plot of respective models. High correlations were observed in the Higuchi (M7, M6, M3, M1), zero-order (M5, M4, M3, M1) and Hixon-crowell (M1, M2, M3, M4) models. To investigate the drug release mechanism, the in-vitro dissolution data were also evaluated by Korsmeyer-peppas model, to find out the diffusional exponent (n) value given in (Table-7), of different formulations was lying between 0.566 -0.912; indicating a non-Fickian Anomalous transport mechanism controlled by swelling and relaxation of polymer. The best fit of release model was Baker-Lonsdale that describes the release rate of drug from a spherical matrix in formulation M3, M4 and M6 that had the greatest correlation coefficient and was confirmed as the most appropriate for describing the release behaviour of T-HCL from spherical polymeric matrix.[15-18]

CONCLUSION

Sustained release microspheres of water soluble drug using hydrophilic-hydrophobic polymeric blend can be successfully prepared by spray-drying with good yield of production, higher drug content, and with better encapsulation efficiency using appropriate spray-drying technological parameters. All formulations have good morphological and dimensional characteristics: spherical shape, smooth surface, and narrow size distribution. From XRD, DSC and FTIR SEM, it could be revealed that T-HCL microsphere formation had different characterizations with compatible formulation also demonstrated a typical sustained release behaviour upto 12h. The best fit of release model was Baker-Lonsdale that describes the release rate of drug from a spherical matrix.

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Table 1: Formulation composition

Batch Code P:P ratio	T-HCL (gm)	HPMC K15M% (w/v)	EudragitR S100 % (w/v)	Water (ml)	Ethanol (ml)
M1 [1:1]	0.2	2	4	100	50
M2 [1:2]	0.2	2	8	100	50
M3 [1:3]	0.2	2	12	100	50
M4 [2:1]	0.2	4	4	100	50
M5 [3:1]	0.2	6	4	100	50
M6 [1:0]	0.2	6	---------	100	-------
M7 [0:1]	0.2	--------	12	-------	50

Table 2: Optimized Spray-drying Conditions Used For Preparing Micropartilces.

Formulations Code	Drying Air Temperature(°C)	Aspirator Capacity (%)	Feed Solution Rate (mL/min)	Compressed Air flow (L/h)
M1 (1:1)	70-75°C	45 %	5 ml / min	200
M2 (1:2)	70-75°C	45 %	5 ml / min	200
M3 (1:3)	70-75°C	50 %	5 ml / min	200
M4 (2:1)	70-75°C	50 %	5 ml / min	200
M5 (3:1)	70-75°C	50 %	5 ml / min	200
M6 (1:0)	90-95°C	50 %	5 ml / min	200
M7 (0:1)	40-45°C	45 %	5 ml / min	200

Table 3: The d90, d50, d10 and span index of the Pure drug (T-HCl) and M3 (1:3) optimized micoparticilate formulation.

Sample	*d*90	*d*50	*d*10	SI (Span Index)
Pure drug	245.05	95.3	6.42	2.50
Formulation M3	132.64	92.32	4.13	1.39

Table 4: Mean particle size, and % product yield of T-HCL loaded Formulations

Formulation code	Polymer blend ratio	Mean particle size (μm)	(%) product yield
Batch M1	1:1	17.05 ± 0.079	23.92 ±5.20
Batch M2	1:2	17.56 ± 0.511	30.42 ±1.32
Batch M3	1:3	13.37 ± 0.058	42.55 ±8.85
Batch M4	2:1	20.59 ± 0.049	28.68 ±4.31
Batch M5	3:1	16.72 ± 0.03	42.41 ±12.31
Batch M6	1:0 (HPMC)	19.37 ± 0.055	34.27 ±8.38
Batch M7	0:1 (Eudragit)	14.78 ± 0.023	39.65 ±2.30

Each observation is the mean ± S.D (n=3) , Mean of 100 particles.

Table 5: The Initial drug loading, Encapsulation efficiency and the % Drug content of T-HCL loaded Formulations

Formulation code	Polymer blend ratio	% intial drug loading	% encapsulation efficiency	% drug content
Batch M1	1:1	15.3±0.82	65.50±3.55	80.85±1.02
Batch M2	1:2	12.4±0.65	82.53±2.12	85.94±1.10
Batch M3	1:3	31.9±0.81	92.22±1.47	90.09±1.43
Batch M4	2:1	18.8±0.34	86.94±1.98	85.79±0.74
Batch M5	3:1	24.2±0.54	94.30±1.90	90.47±0.68
Batch M6	1:0 (HPMC)	21.0±0.22	81.22±0.84	87.95±0.68
Batch M7	0:1 (Eudragit)	19.0±0.47	74.98±2.04	88.93±0.51

Each observation is the mean ± S.D (n=3).

Table 6: Dissolution Parameters for Microparticle Formulations

Batches	% Dissolution Efficiency	MDT (min)	*f1*	*f2*
M1	63.19%	319	18.45	50.41
M2	65.73%	412	22.31	46.01
M3	80.16%	425	10.24	62.19
M4	60.30%	372	23.78	45.15
M5	65.90%	381	15.63	59.06
M6	57.71%	192	15.72	42.97
M7	59.62%	204	18.26	58.94
Marketed	81.67%	337		

Table 7: Regression Parameters of Various Batches after Fitting Drug Release Data (Obtained in D.W.) to Various Release Kinetic Model

Formulation Code	Zero-order model		First-order model		H-M model		H-C model	P-K model				B & L model	
Batches	R	K_0	R	K_1	R	K_h	R	K_{hc}	R	K_{pk}	N	R	B
M1 (1:1)	0.987	8.339	0.785	0.126	0.974	35.18	0.990	0.208	0.995	0.934	0.875	0.801	0.025
M2 (1:2)	0.975	9.039	0.784	0.082	0.915	37.28	0.985	0.159	0.986	1.013	0.912	0.718	0.015
M3 (1:3)	0.952	6.502	0.890	0.049	0.975	28.74	0.984	0.184	0.995	0.698	0.566	0.992	0.014
M4 (2:1)	0.991	8.861	0.872	0.064	0.961	34.60	0.981	0.211	0.990	1.070	0.970	0.902	0.013
M5 (3:1)	0.997	8.396	0.812	0.101	0.952	32.87	0.958	0.240	0.964	0.834	0.731	0.907	0.014
M6 (1:0)	0.960	16.99	0.850	0.251	0.985	51.04	0.974	0.196	0.980	0.397	0.597	0.864	0.021
M7 (0:1)	0.935	10.23	0.983	0.191	0.980	37.14	0.969	0.228	0.980	0.753	0.854	0.768	0.017

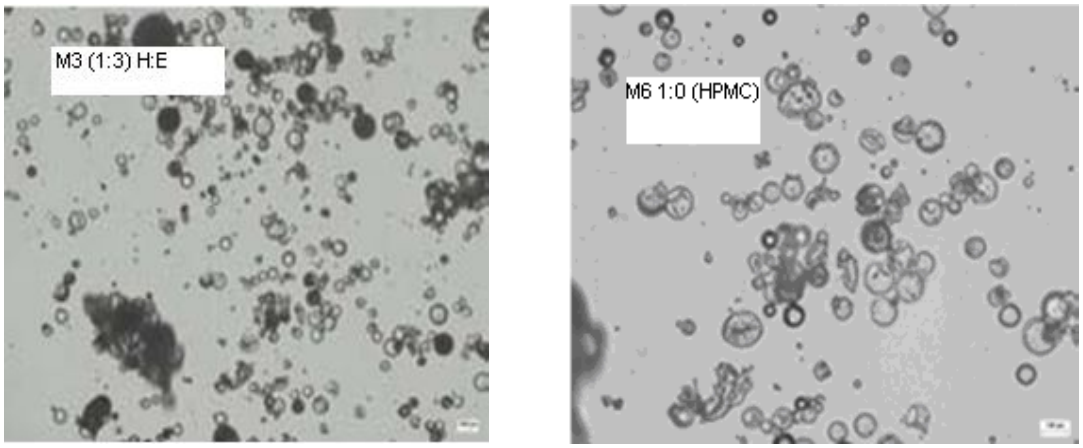

Fig. 1: Photomicrograph of Microsphere Obtained Using (a) Polymeric Blend Ratio (1:3) and (b) HPMC alone (1:0)

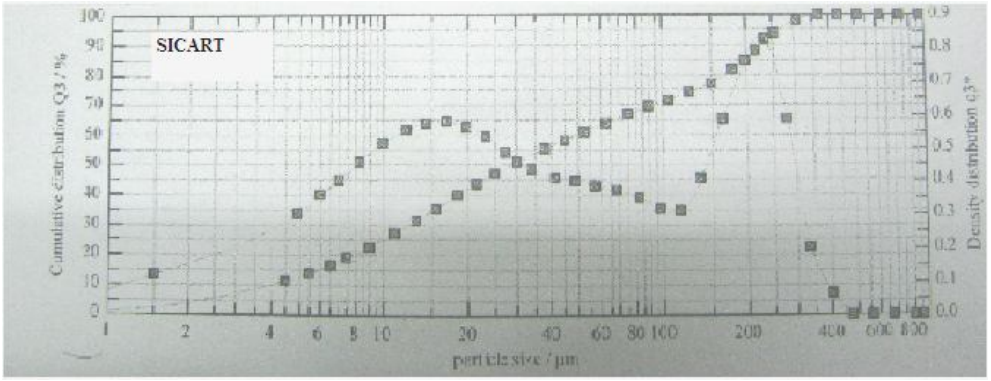

Fig. 2: Particle Size Distribution of Pure Drug Compared with Drug Loded Microparticles

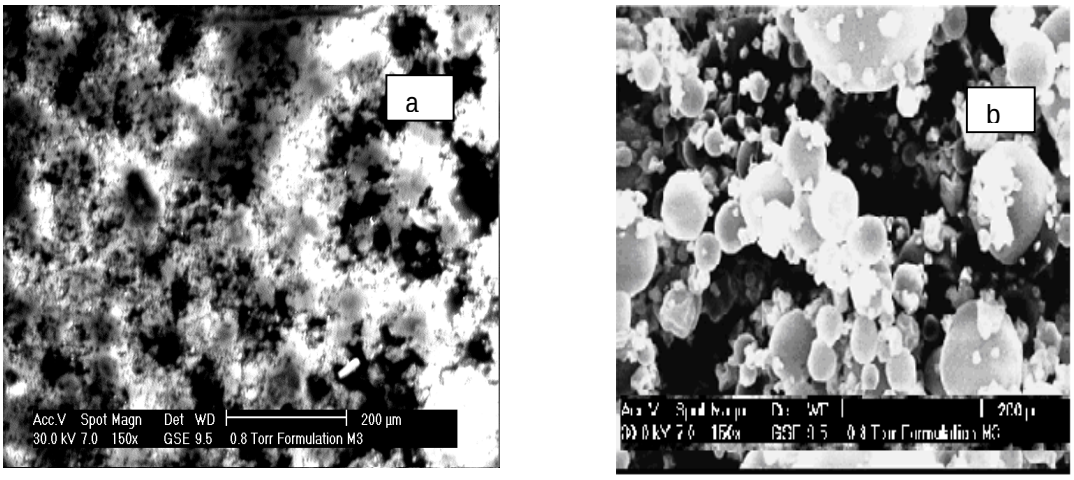

Fig. 3: SEM Images of Optimized Formulation M3 (1:3) at Different Magnification (a) 150x, (b) 50x

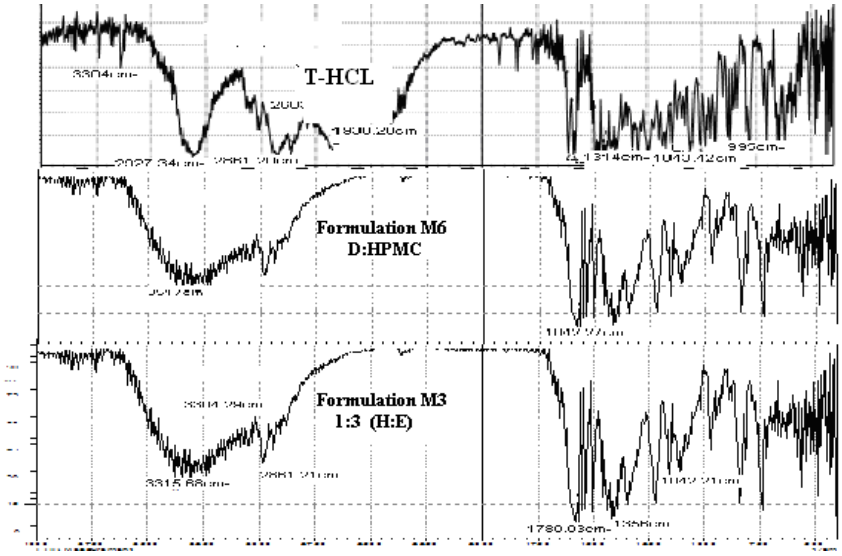

Fig. 4: FTIR Spectra of Pure Drug and Optimized Formulations

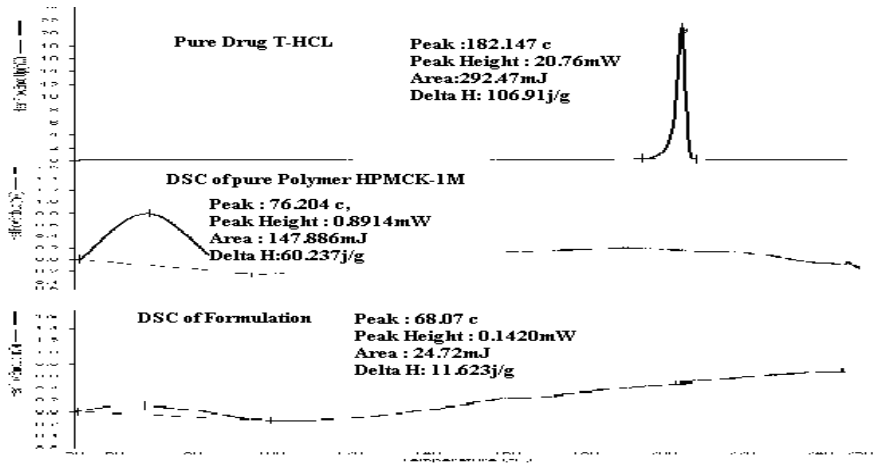

Fig. 5: DSC Thermogram of Pure Drug, Polymer and Drug Loded Micropartilces

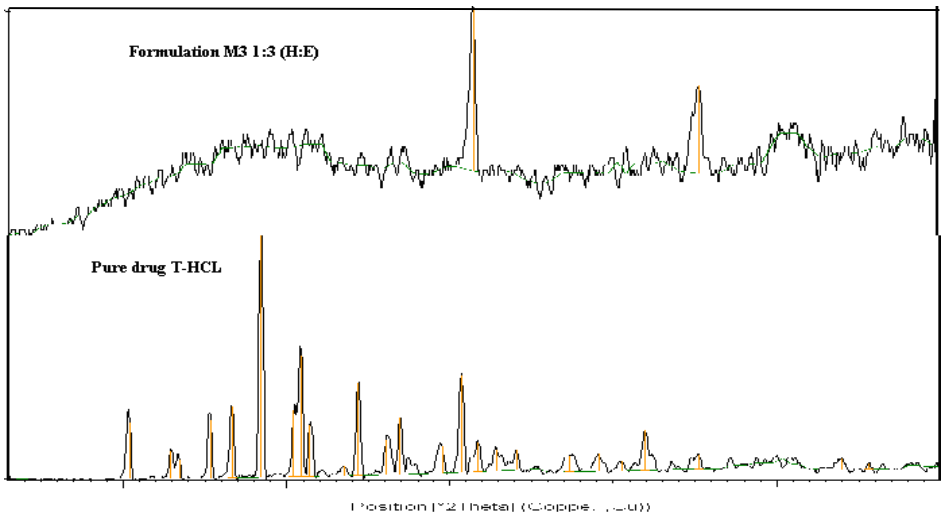

Fig. 6: X-ray Diffractogram of Pure Drug T-HCl and Drug Loded Microparticles

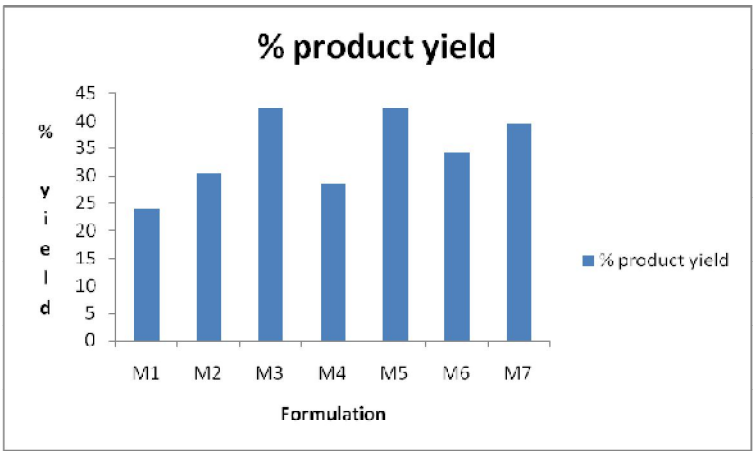

Fig. 7: Graphical Representation of Effect of Different Fromulations on Product Yield

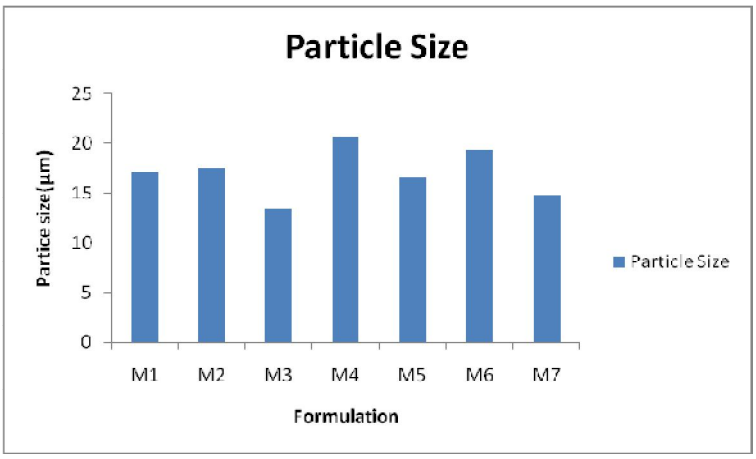

Fig. 8: Graphical Representation of Effect of Different Fromulations on Particle Size

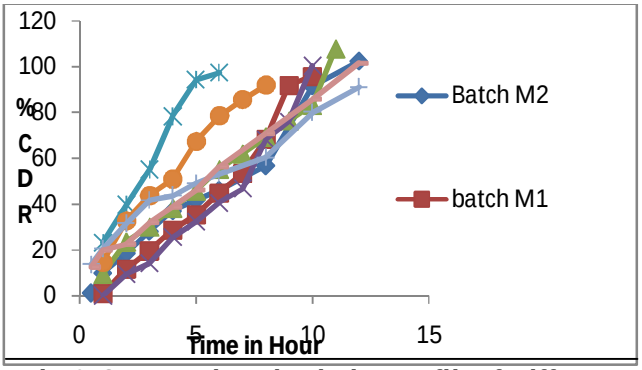

Fig. 9: Comparative Dissolution Profile of Different Batches of Microspheres