



Formulation Design and Evaluation of Solid Lipid Micro-particles of Curcumin for the Treatment of Alzheimer's disease

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ABSTRACT

Solid lipid microparticles reach the site of its action in a controlled rate and do show controlled release for a better therapeutic result. A good drug carrying and release system involve a controlled drug delivery that improves bioavailability, to enrich stability and to minimise the toxic effects followed with a targeted drug at the site of its action. The solid lipid microparticles of curcumin were prepared in a view to achieving high permeability of curcumin in the brain through blood-brain-barrier. The lipid microsphere solids were prepared by hot melts microencapsulation technique to formulate solid lipid microspheres. Twelve lipid formulations were prepared with varying concentration of surfactants (span 40, span 70, span 90 and Tween 100). The developed formulation was subjected to various parameters such as the particle size, % entrapment efficiencies, yield productions, % cumulative release, percentage yield and drug loading, based upon highest entrapment efficiency, drug release and % cumulative release, the F₃ formulation was considered as the best formulation. The prepared microsphere was subjected to different evaluation parameters such as thin-layer chromatography, melting point, FTIR, solubility, compatibility study and In-vitro drug release. The developed formulation shows spherical and smooth surface. The percentage release of drug F₃ formulation has been found highest of about 86.23% after 12 hr.



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spherical microparticles of lipid with a size range of 1-1000 μ m can be suspended in a suitable aqueous solvent system offer possible new ways to develop an improved new therapeutic product (Ojha, 2014). The incorporation of the drug in a microcarrier form leads us to develop a new drug delivery system for a designed site targeting. So the microparticles of lipid reach the target site in a controlled manner and a good rate for better therapeutic results. The drug delivery system could be made for prolonged sustained drug delivery, improved bioavailability, enhanced stability and for reduced toxic effects follows a targeted drug for a specific site (Jithan *et al.*, 2012).

INTRODUCTION

Solid lipid microparticles were firstly developed in 1990 and are considered a promising drug carrier system, especially for the introduction of the active drug substance and to carry and finally release for controlled drug delivery (Pilaniya *et al.*, 2011). The

Microparticles are made mostly from two types of polymers, natural polymer or synthetic polymer that could assist the transportation of active compound. Ethylcellulose and sodium alginate natural polymers could be obtained from the marine brown

algae, which are biodegradable, biocompatible, and non-toxic, are widely used for the preparation of oral and topical formulations (Patel *et al.*, 2012). Biodegradable microspheres capsules can be used more often as a support for the delivery of bioactive compounds. A well designed and a controlled drug delivery system is the one which enhances the maximum therapeutic efficacy, necessary to deliver the drug to the target site in an appropriate amount and at the right time with maximum therapeutic effects and least side effects (Kataria *et al.*, 2011). There are many methods which are used for the preparation of solid lipid microparticles (SLMs) include homogenisation technique, solvent evaporation technique, solvent extraction technique, encapsulation technique, phase Separation Co-acervation technique, spray drying method (Kumar *et al.*, 2011).

A large number of analytical techniques could be used for the characterisation of microspheres like scanning electron microscopy technique, differential scanning calorimetric technique and Fourier transformed infrared spectroscopy (FTIR). FTIR mainly is used for the analysis of drug-loaded formulation. The *in-vitro* drug release was studied using rotator basket method with the help dissolution apparatus at 150 rpm in a phosphate buffer solution having pH 7.4 (Jaspart *et al.*, 2005; Kaur *et al.*, 2012; Bharat *et al.*, 2006). Curcumin, 1, 7-bis (4-hydroxy-3-methoxyphenyl) -1, 6- heptadiene-3, 5- dione), is a small molecular weight, a natural hydrophobic polyphenolic compound, from the rhizomes of *Curcuma longa*, family Zingiberaceae whose structural formula was first described in 1910 by Lampe and Milobedesk (Prashar *et al.*, 2011).

Various curcuminoids are found in curcumin. The curcuminoids founds are about 5% bisdemethoxycurcumin, 15% demethoxycurcumin, and 80% Curcumin. When curcumin is taken orally, 75% of it excreted in the faeces while only traces of curcumin appear in Urine. The long list of uses of curcumin includes antioxidant, anti-inflammatory, anti-cancer, antimalarial, antiseptic, rheumatism arthritis, asthma, diabetes, analgesic and wound healing activities (Eryanti *et al.*, 2012).

Curcumin has shown an effective therapeutic agent and defence mechanism against Alzheimer's disease by the ability to destabilize α , β plaque formation and through increase the phagocytosis of α , β plaque (Naama *et al.*, 2010).

MATERIALS AND METHODS

Preformulation study of curcumin

In Preformulation study, the physicochemical prop-

erty of the active compound could affect the drug performance for development of efficient, safe and stable dosage form.

It is an optimising process in which studies could help in rational designing of the formulation. The Preformulation study involves the organoleptic character analysis of active compound which may include: order, colour, taste, solubility, melting point, entrapment efficacy, compatibility study, pharmacokinetic study, thin layer chromatography and calibration curve. These studies reduce the chances of error of any kind of incompatibility during formulation.

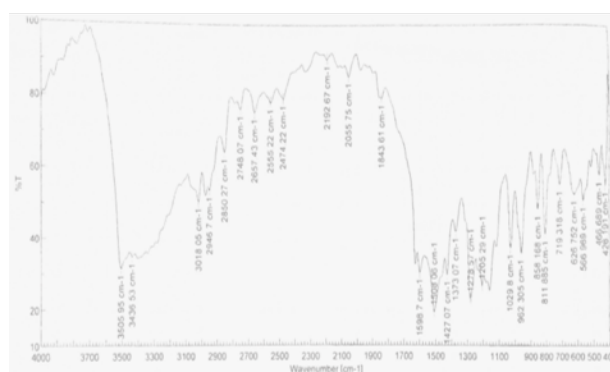


Figure 1: Reference FTIR Spectra of Curcumin

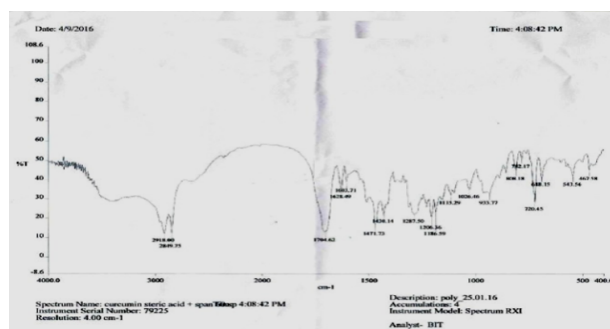


Figure 2: FTIR of Curcumin + Stearic Acid + Span 70

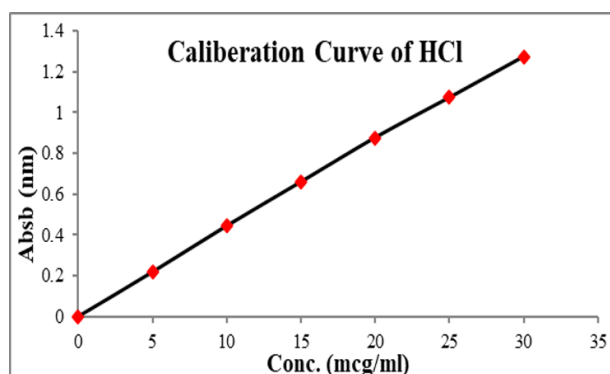


Figure 3: Standard Plot of Curcumin in 0.1 N HCl (1.2pH) at λ_{max} 432nm.

Table 1: The Melting Point of curcumin

Method Used	Experimental Value	Observed Value
Capillary Fusion Method	182°C ± 1.28	180°C ± 17.9

Table 2: Thin Layer Chromatography

Thin-layer chromatography	Rf Value (Observed)	Reference Value (n=3)
Curcumin	0.87	0.90

Table 3: Composition of curcumin targeted Solid lipid microparticles

Formulation	Drug(mg)	Stearic acid	Surfactant Span 90
F1	125	2	0.5
F2	125	2	1.0
F3	125	2	1.5
			Span 70
F4	125	2	0.5
F5	125	2	1.0
F6	125	2	1.5
			Span 40
F7	125	2	0.5
F8	125	2	1.0
F9	125	2	1.5
			Tween 100
F10	125	2	0.5
F11	125	2	1.0
F12	125	2	1.5

Table 4: Interpretation of FTIR (drug)

Reported(cm ⁻¹)	Wave No(cm ⁻¹)	Functional group	Inference
3510.2cm ⁻¹	cm ⁻¹	OH Phenol	Stretching
1627.8cm ⁻¹	cm ⁻¹	C=O Ketone	Stretching
1596cm ⁻¹	cm ⁻¹	C=C Aromatic	Stretching
1276cm ⁻¹	cm ⁻¹	C-O	Stretching

Table 5: Calibration curve data of curcumin in 0.1N HCl (1.2pH) at Max 432nm

S. No.	Conc. (µg/ml)	Absorb at λ _{max} 432 nm
1	5	0.218 ± 0.004
2	10	0.452 ± 0.003
3	15	0.665 ± 0.002
4	20	0.884 ± 0.004
5	25	1.072 ± 0.003
6	30	1.251 ± 0.002

Table 6: Calibration Curve data of Curcumin in Phosphate Buffer (7.4pH) at λ_{max} 432nm

S. No	Conc. ($\mu\text{g/ml}$)	Absorb at λ_{max} 432nm
1	5	0.222 ± 0.005
2	10	0.451 ± 0.003
3	15	0.671 ± 0.004
4	20	0.875 ± 0.002
5	25	1.099 ± 0.004
6	30	1.323 ± 0.005

Table 7: Solubility of Curcumin

Solubility Study	Conc. (mg/ml)	Solubility Study	Conc. (mg/ml)	Solubility Study	Conc. (mg/ml)
Methanol	4.21 ± 0.056	Phosphate Buffer	2.68 ± 0.039	0.1N HCl	0.65 ± 0.06

Table 8: Drug loading, Percentage yield data

S. No	Formulation code	Drug loading (%)	Entrapment efficiency (%)	Percentage yield (%)
1	F1	53.34 ± 0.43	60.56 ± 0.85	82.37 ± 0.39
2	F2	68.27 ± 0.89	71.89 ± 0.34	85.69 ± 0.47
3	F3	72.71 ± 1.05	89.32 ± 0.76	89.38 ± 0.58
4	F4	40.00 ± 0.32	59.83 ± 0.94	72.45 ± 0.79
5	F5	54.46 ± 0.54	67.90 ± 0.34	74.56 ± 0.91
6	F6	74.65 ± 0.85	81.02 ± 0.87	79.78 ± 0.35
7	F7	20.12 ± 0.99	48.34 ± 1.54	53.45 ± 0.73
8	F8	35.93 ± 0.36	54.76 ± 0.34	60.05 ± 0.87
9	F9	47.20 ± 0.59	63.95 ± 0.54	66.21 ± 0.21
10	F10	20.00 ± 0.87	30.00 ± 0.87	60.07 ± 0.43
11	F11	21.49 ± 0.23	37.49 ± 0.23	68.56 ± 0.98
12	F12	25.50 ± 0.76	45.60 ± 0.76	72.89 ± 0.26

Table 9: Average Weight Uniformity of SLMs

S. No	Formulation code	Average weight (mg)
1	F1	2790
2	F2	2324
3	F3	2921
4	F4	2072
5	F5	2177
6	F6	2611
7	F7	2245
8	F8	2098
9	F9	2181
10	F10	2295
11	F11	2130
12	F12	2503

Table 10: In-vitro Drug Release of Curcumin microsphere Formulation from (F₁-F₁₂)

Hr	F1	F2	F3	F4	F5	F6
1	11.23±0.38	12.32±0.32	23.02±0.56	08.79±0.78	09.01±0.85	11.03±0.49
2	15.85±0.67	20.74±0.84	39.56±0.64	12.56±0.89	13.98±0.64	34.85±0.67
3	25.79±0.59	35.47±0.56	48.75±0.38	28.02±0.34	15.44±0.67	42.5±0.89
4	37.23±0.81	40.65±1.22	60.89±0.94	38.52±0.56	16.79±0.94	55.85±0.29
5	48.23±0.87	46.89±0.72	73.05±1.05	42.89±0.78	17.07±0.92	68.57±0.38
6	55.45±0.48	52.74±0.29	78.96±0.98	62.12±0.98	24.12±0.28	75.07±0.91
7	60.22±0.62	57.98±0.62	80.63±0.82	51.59±1.23	28.18±0.48	79.56±1.05
8	64.78±1.24	63.45±0.67	81.36±0.61	58.27±0.58	40.71±1.25	80.14±0.54
9	67.36±0.87	68.55±0.78	82.25±0.31	61.77±0.89	52.74±0.37	81.54±0.76
10	67.91±0.74	72.45±1.08	84.23±1.04	67.65±1.09	67.65±1.09	82.21±0.98
11	71.23±0.39	75.23±0.49	85.89±0.67	70.08±0.55	75.81±0.83	83.36±0.34
12	73.37±0.82	78.95±0.67	88.12±0.82	75.19±0.87	79.01±0.68	85.15±0.55
Hr	F7	F8	F9	F10	F11	F12
1	2.21±0.27	10.56±0.2	17.5±0.81	1.59±0.08	1.88±0.12	11.03±0.49
2	13.59±0.84	14.85±0.67	26.4±0.97	8.62±0.66	2.95±0.76	10.18±0.90
3	15.78±0.64	15.98±0.98	32.2±0.21	18.02±0.28	3.27±0.94	19.06±0.35
4	17.19±0.49	17.76±0.46	44.12±0.62	25.79±0.87	4.56±0.58	28.62±0.63
5	21.25±0.76	20.46±1.03	59.75±1.06	33.12±0.97	10.25±1.04	37.49±0.57
6	23.49±1.21	34.76±0.98	67.22±0.82	37.62±1.20	14.29±0.45	41.13±0.26
7	35.76±0.84	42.16±0.76	70.27±0.94	44.71±1.66	27.49±0.68	47.56±0.36
8	42.18±0.49	49.25±0.44	74.87±0.27	47.93±0.75	31.76±0.97	52.22±0.79
9	53.64±0.64	59.45±0.69	77.21±0.68	53.17±0.62	44.26±1.36	57.83±0.98
10	62.35±0.76	69.75±0.84	80.23±1.11	56.06±0.36	50.72±0.56	62.11±1.34
11	70.25±1.04	79.12±0.55	82.36±0.94	63.29±0.59	60.28±0.76	65.27±0.64
12	77.29±0.94	82.26±1.01	84.21±0.87	62.33±1.87	65.46±0.98	69.87±0.71

Table 11: In-vitro Drug Release of best four formulations (F₃, F₆, F₉ and F₁₂)

Hour (Hr)	F3	F6	F9	F12
0	0	0	0	0
1	23.2±0.56	11.03±0.49	17.5±0.81	3.07±0.54
2	39.56±0.64	34.85±0.87	26.4±0.67	10.18±0.90
3	48.75±0.38	42.5±0.38	32.2±0.47	19.06±0.25
4	60.89±0.94	55.85±0.29	44.12±0.28	28.62±0.63
5	73.05±1.05	68.57±0.68	59.75±1.05	37.49±0.57
6	78.96±0.98	75.07±0.91	67.22±0.98	41.13±0.26
7	80.63±0.82	79.56±0.47	70.27±0.82	47.56±0.65
8	81.36±0.61	80.14±0.67	74.87±0.61	52.22±0.36
9	82.25±0.38	81.54±0.28	77.21±0.38	57.83±0.79
10	84.23±1.04	82.21±1.11	80.23±1.04	62.11±0.18
11	85.89±0.67	83.36±0.67	82.36±0.67	65.27±1.36
12	88.12±0.82	85.15±0.82	84.21±0.82	69.87±0.71

Table 12: Kinetic assessment of curcumin loaded microspheres (F₃)

Formulation Code	Correlation co-efficient R2 value			
	Zero order (R2)	Zero order (R2)	Higuchi type (R2)	Korsmeyer Pepper release
F3	0.8955	0.8311	0.9221	0.8719

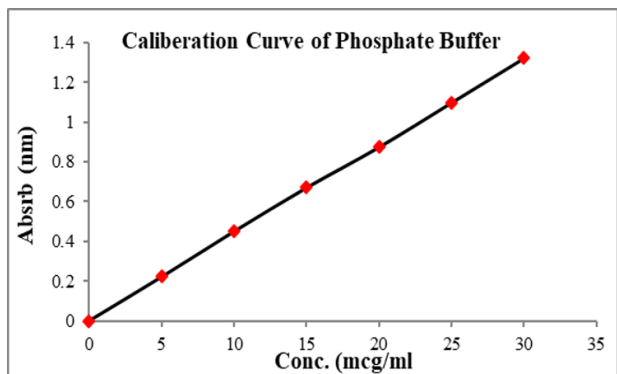


Figure 4: Standard Plot of Curcumin in Phosphate Buffer (7.4pH) at λ_{max} 432nm

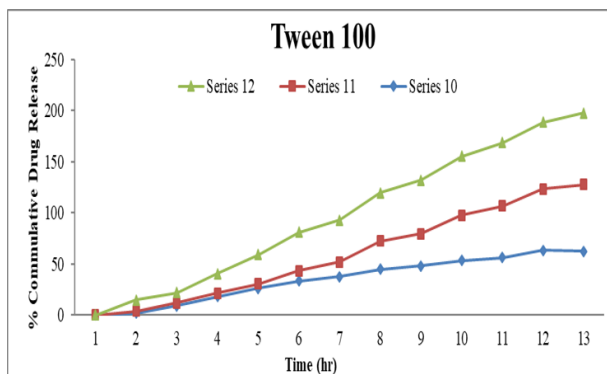


Figure 8: % Cumulative Drug Release of surfactant Tween₈₀ formulations (F₁₀-F₁₂)

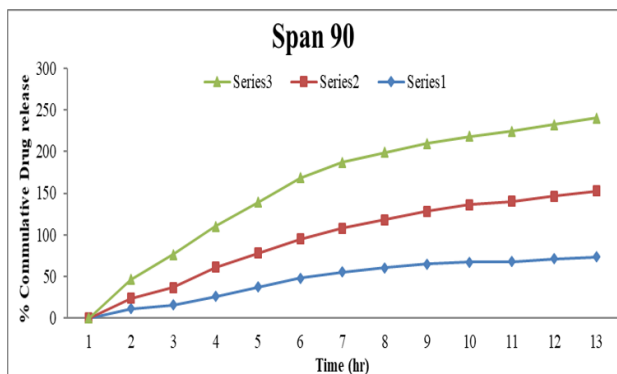


Figure 5: % Cumulative Drug Release of surfactant span 90 formulations (F₁-F₃)

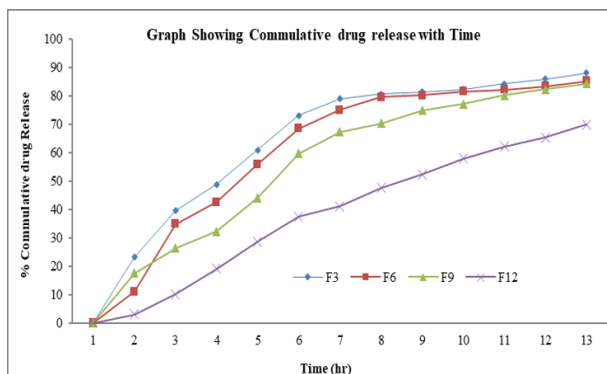


Figure 9: % Cumulative Drug Release of the best four formulations (F₃, F₆, F₉ and F₁₂)

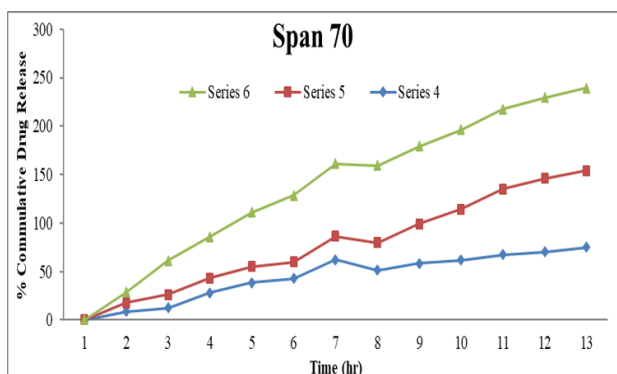


Figure 6: % Cumulative drug release of surfactant span 70 formulations (F₄-F₆)

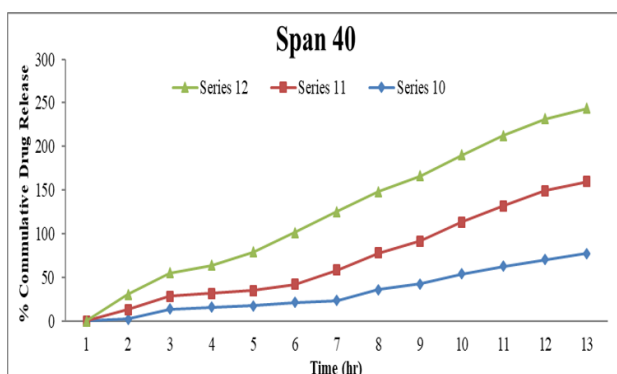


Figure 7: % Cumulative Drug Release of surfactant span 40 formulations (F₇-F₉)

Authentication of the procured curcumin

Several parameters are taken into consideration for the authentication of the drug.

Melting point

The Melting point study of the drug was determined by capillary fusion method.

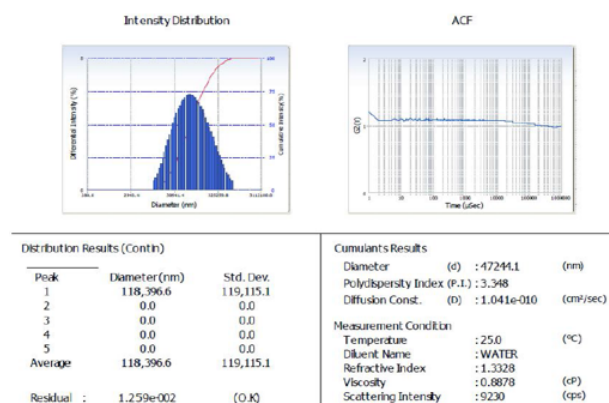


Figure 10: Schematic Representation of Particle size of formulation F3

Thin-layer chromatography (TLC)

The TLC plate was prepared by coating with Silica G. A spot of test solution is then applied on the sil-

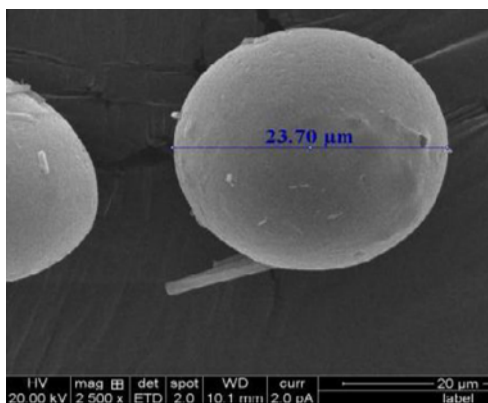


Figure 11: SEM image (shows the morphology of microparticle) of curcumin solid lipid microparticles

ica plate, just above 0.5cm from the bottom and then placed in a TLC chamber, which was saturated with a solvent system containing chloroform: benzene: methanol (80:15:5).

Fourier Transforms Infra-Red Spectroscopy (FTIR)

The FTIR spectra are recorded in the range (4000 – 400) cm^{-1} . The sample mixed with KBr was recorded after compressed into a tablet. The drug KBr pellet was analysed for the spectra (Josephine *et al.*, 2011).

Preparation of Solid Lipid Microparticles

Hot melt microencapsulation technique

Solid Lipid Microparticles (SLMs) are prepared by hot-melt microencapsulation technique (phase inversion technique). Stearic acid was melted in a beaker on a hot plate at 70°C. Curcumin was added to the melted stearic acid while stirring on magnetic stirrer to form hot melt mixture. The mixture was emulsified into an aqueous surfactant solution and was heated above the lipid melting point to form oil/water emulsion. Different surfactant grades (Span 40, Span 70, Span80 and Tween 100) were used at different concentrations (0.5 ml, 1 ml, 1.5 ml). The oil-water emulsion was poured into 100 ml of ice-cooled aqueous phase maintained at 2°C-5°C and was finally allowed to cool in an ice bath. Hardened microparticles are allowed to settle, and then after 15 minutes aqueous phase was decanted, microparticles are filtered, rinsed with water, froze and finally dried (Kumavat *et al.*, 2013).

In-vitro drug release

In-vitro drug release study used 0.1N HCl (pH 1.2) and phosphate buffer (7.4pH) in dissolution medium (900ml). Sample withdrawn from dissolution medium was analysed by UV spectrophotometer at 432nm.

Observation Results

Preformulation study of curcumin

Preformulation study determines the physicochemical property of the active compound that affects the drug performance and product development, safe and stable dosage form. The study in reference avoids the chances of error and incompatibility during formulation.

Authentication of the procured curcumin

Several parameters are taken into consideration for authentication of the drug.

Melting point

The Melting point of the drug as determined by capillary fusion method shows in Table 1.

Thin-layer chromatography (TLC)

As per the TLC, the R_f value as observed is shown in Table 2.

Solid lipid Microparticles via Hot melt microencapsulation technique

The curcumin composite Solid lipid microparticles are as shown in Table 3.

Fourier Transforms Infra-Red Spectroscopy (FTIR)

The FTIR graph as obtained is shown below, and the obtained value is shown in the Table 4.

Calibration Curve of Curcumin in Phosphate Buffer (7.4pH)

Calibration curve of curcumin was plotted in phosphate buffer (7.4pH) at λ_{max} 432nm, and the results are shown in Table 6.

Development of curcumin loaded microspheres.

Various formulation batches were formulated successfully using hot-melt microencapsulation technique. The technique uses curcumin with 2gm Stearic acid, and different amount of surfactant melts in a beaker at 70°C. The oil/water emulsion is formed then poured in 100 ml of ice-cooled aqueous phase at 2°C- 5°C and was allowed to cool in an ice bath.

Evaluation Parameter

Evaluation of Solid lipid microparticles (SLMs) was evaluated for various parameters which are as:

Drug loading, Percentage Yield and Entrapment efficiency

Drug loading, Yield and entrapment efficiency was carried out on twelve formulations, an assay for drug loading, Percentage yield and entrapment efficiency determination was done by using UV spectrophotometer. The % drug loading was found 54.63 to

67.78%, Percentage yield as determined 72.01 to 79.64, and entrapment efficiency was found 82.23 to 88.56 as given in Table 8.

Weight Uniformity

Weight individual formulations of curcumin microsphere are checked for weight uniformity.

In-vitro drug release

In-vitro drug release study as carried out using 0.1N HCl (pH 1.2) and phosphate. The drug release profile of various formulations (F₁-F₃) of surfactant Span 90, (F₄-F₆) of surfactant Span 70 in Table 9 and, (F₇-F₉) of surfactant Span 40, (F₁₀-F₁₂) of surfactant Tween₈₀ in Table 10. Based on encapsulation efficiency, percentage yield and percentage drug release, the optimised formulations are F₃ and F₂. Therefore, F₃ formulation was selected for measuring the size and shape of the microsphere.

Kinetic release of curcumin loaded microspheres

Different models were used for the release of F₃ formulation and best fit method as found was Higuchi method.

The particle size of microparticles:

The formulation Malvern Zeta analysed F3 microparticle size- Sizer, which provides the average size of microparticles which ranged as 23.70 μ m. The particle size is shown in the Figure 10.

Morphology of Solid lipid microparticles

Scanning electron microscopy (SEM) was used for the morphology determination of Solid lipid microparticle. As per the SEM analysis, the optimised F3 formulation is smooth and spherical. The outer surface of SLM is shown in Figure 11.

DISCUSSION

Curcumin microspheres were designed for controlled and targeted release of drug to the brain, in which stearic acid polymer with various grades of surfactant (Span 40, 60, 80 and Tween 100) were chosen which assists the drug transportation and also provides a targeted effect (Table 3). Melting point determination which was referenced from the literature was used for the identification of the procured drug. The TLC and Rf values were almost the same as reported in the literature which confirmed the identity of the drug (Table 1 & Table 2). Further identification of the drug was confirmed by FTIR spectroscopy which confirms the presence of various functional groups present in curcumin as reported in the literature (Figure 1 & Figure 2) (Table 3). During drug-excipient compatibility study

by FTIR, there was no change in the major peaks (Table 4) which suggests no interaction between drug and excipient. Regarding solubility studies in different media, it was found that solubility of curcumin (Table 7) was more in methanol (4.21 \pm 0.056) than Phosphate Buffer pH 7.4 (2.68 \pm 0.039) and pH 1.2 (0.1N HCl). It was observed that the results of percentage yield and drug loading were within the limit concerning the variation of surfactant concentration of the same formulations. The encapsulation efficiency of all formulations lays 82.23% to 88.56%, Percentage yield was 72.01%-79.64%, and drug loading was found to be 54.63% to 67.78% (Table 8). The drug release pattern of curcumin via in-vitro method shows that F3 formulation showed full release of up to 86.23%. The Span 90 containing microspheres of curcumin offered a high degree of favourable results in the relation of its constant drug release (Table 10, Figure 5, Figure 6, Figure 7 & Figure 8).

The average size of F3 formulations was found to 23.70 μ m (Table 11 and Figure 9). The results of Scanning Electron Microscopy revealed the smooth and spherical structure of microsphere. The Preformulation study for drug authentication was carried out by melting point determination, thin layer chromatography and FTIR spectroscopy. As per the compatibility study, no change in the drug and excipient has been found, which means drug does not show any kind of incompatibility with the recipient (Table 12). The calibration curve of curcumin was prepared in 0.1N HCl (pH 1.2), (Table 5 and Figure 3) phosphate buffer (pH 7.4) (Table 6 and Figure 4) and methanol. Curcumin SLM consists of a varied ratio of surfactant but the constant ratio of the polymer. The developed formulation was evaluated in terms of particle size, shape, drug loading, efficient entrapment, percentage yield, drug release and kinetic release of the drug (Figure 10). The SEM of curcumin microparticles reveals the spherical and smooth surface (Figure 11). All the formulation shows good entrapment efficiency. The USP-2 dissolution apparatus carried out the microparticle in-vitro release. The study showed that there was an abrupt release of drug in 12hr from the Microparticle formulation and the formulation was analysed by various kinetic models like zero order, first order, Hiruchi and Pappas model.

CONCLUSION

In conclusion, it could be concluded that the drug formulation was found to be good in every respect as per the formation, particle size and distribution of particles are taken into consideration. The devel-

oped formulation of curcumin showed that the drug release and kinetic release is as per the standard drug, so the formulation in reference can be best used for the development of drug-related to mental health. The in-vitro studies showed that drug could be made to release at a targeted point in about 12hrs. So overall, a suitable formulation can be prepared by using curcumin for the development of any sort of drug.

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Conflict of Interest

There is no conflict of interest between the authors nor outside.

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