Original Article

Formulation and Evaluation of Carbamazepine Tablets using Biosurfactant in Ternary Solid Dispersion System

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ABSTRACT

Objectives: The present study is aimed to develop and evaluate Carbamazepine tablets using ternary solid dispersed product. Carbamazepine belongs to BCS class II having low solubility. Ternary system was formulated with biosurfactant and water-soluble polymers to enhance dissolution rate and bioavailability. **Methods:** Binary and ternary solid dispersion was prepared using hydroxyl propyl methyl cellulose (HPMC) K-100, Polyvinyl pyrolidine (PVP) K-30 and Poly ethylene glycol (PEG) 6000 as a polymer and biosurfactant respectively by solvent evaporation method and evaluated for drug content uniformity and *in-vitro* dissolution study. Carbamazepine tablet were prepared by incorporation of ternary solid dispersed product along with other excipients by direct compression technique. Prepared formulations were evaluated for pre-compression and post-compression parameters. Oral toxicity study of biosurfactant was performed using female wistar rats. **Results:** *In-vitro* dissolution profile of optimized tablet formulation OF1 and OF2 showed 75.14% and 71.26% release in 1.2 pH respectively and similarly at 6.8 pH buffer 64.33% and 58.96% respectively. Pre-compression and post-compression values of formulated tablets were within the specified acceptable limits. *In-vivo* dissolution study of optimized formulation OF1 showed an increase in dissolution rate in accordance with pure drug. Oral toxicity study of biosurfactant was safe at 2000 mg per kg body weight of rat. Short term stability of the optimized formulation was stable without deviations at room temperature. **Conclusion:** Addition of biosurfactant in ternary solid dispersion system proved to be promising excipient in formulation of carbamazepine tablet for enhanced dissolution rate, dose reduction and bioavailability.

Key words: Carbamazepine, Solid dispersion, Ternary system, Biosurfactant, *in-vivo* oral toxicity.

INTRODUCTION

Carbamazepine is an antiepileptic drug belonging to Biopharmaceutical Classification System (BCS) class II drug with low solubility in biological pH fluids.[1] Solubility enhancement is an important for the drug delivery into fluid media. Novel technology has been developed such as Micronization, Solid dispersion, Beta-cyclodextrine complexation. Solid dispersion is most commonly used technique to enhance solubility by increasing dissolution rate and bioavailability. Ternary system is an advanced method of solid dispersion technique involves addition of surfactants in binary system, to enhance solubility of poorly water-soluble drug.[2,3] In ternary phase the different synthetic surface active agents are used in the concentration of 0.5% to 20%w/w, mainly non-ionic surfactants but the number of fold increase in dissolution rate is too or three folds in comparison with pure poorly soluble drug.[3-5]

Different novel class of biosurfactant were prepared by biotechnological technique

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using different carbon and nitrogen sources with additives from specific micro-organisms. The basic composition of biosurfactant is fatty acid with amino acid and mono or disaccharides. The major advantage of biosurfactant over synthetic surfactant are high emulsifying index, stable at all pH and temperature, lowest toxicity, Biodegradability, water penetrability and salinity.[5]

Our present study aimed to formulate carbamazepine tablet with enhanced dissolution rate using solid dispersion technique. Binary and ternary systems was developed with water-soluble polymers, HPMC, PEG 6000 and biosurfactant, poloxamer 407 respectively. The effect of biosurfactant was evaluated by *in-vitro* dissolution study. Biocompatibility of biosurfactant was evaluated by oral toxicity study in rats.

MATERIALS

Carbamazepine was procured as gift sample from Zydus Cadila Ltd. Goa. Poloxamer 407 from Balaji drugs. Poly-ethylene Glycol (PEG 6000) from Sigma-Aldrich-Bangalore. Rhamnolipids 90 % from AGAE Technologies, Corvallis. Hydroxypropyl methyl cellulose (HPMC) from Colorcon industry, Goa. Lactose, Magnesium stearate, Talc and Cross-carmallose from Himedia Lab Pvt. Ltd-Mumbai. All other chemicals from S.D Fine Chemicals Pvt. Ltd.-Mumbai (AR grade).

METHODS

Compatibility Studies

Compatibility study of drug and excipients was carried out through Fourier transmission infrared spectrophotometer (FTIR) (Shimadzu Japan) using potassium bromide scanned from 400-4000 cm^{-1}. Graphs were recorded and analyzed for comparative compatibility studies.[6,7]

Differential Scanning Calorimetric (DSC) analysis were conducted to study the interaction between Carbamazepine and polymers. Samples were placed in an aluminum pan and heated at a rate of 10°C/min in the temperature range of 30-300°C. Empty pan was used as reference and thermal analysis was performed under nitrogen atmosphere The heat flow was measured for both Polymer-drug and was observed for endothermic peaks.[6,7]

Solubility Analysis

Saturation solubility was performed using metabolic shaker for 24 hr at room temperature. Solvents used were 1.2 pH and 6.8 pH buffers. Drug content analysis was performed using UV Spectrophotometer at λ_{max} 285nm.

Preparation of Binary and Ternary Solid dispersion

Binary and ternary solid dispersion was prepared by solvent evaporation technique with different ratio (Table 1). The water-soluble polymers (HPMC, PVP, PEG) and drug were dissolved in solvent using magnetic stirrer with 50 rpm at room temperature for 1 hr till clear solution was obtained. Solution were evaporated on water bath at 60°C temperature till solid mass was formed and passed through the 60 # mesh, stored in air tight container. Ternary solid dispersion was also prepared with similar steps of binary system with addition of biosurfactant and poloxamer 407. Shown in Table 2.[6,7]

Evaluation of Binary and Ternary Solid Dispersed Product

Drug Content

Binary and ternary solid dispersion products drug contents were determined by dissolving the weighed quantity of solid dispersed product in pH 1.2 and 6.8 pH buffers separately, filtered and analyzed for its drug content at λ_{max} 285nm using UV Spectrophotometer.[6,7]

In-vitro Dissolution Study

All solid dispersion products and pure drug were subjected for dissolution profile using USP dissolution apparatus (type II) at temperature 37±0.50°C, at 50 rpm in 1.2 pH buffer media for 1 hr. Aliquot samples were withdrawn from 900 ml at specified intervals, filtered and analyzed at λ_{max} 285 nm using UV spectrophotometer and sink condition was maintained.[6,7]

Preparation of Carbamazepine Tablet Using Solid Dispersed Product

Carbamazepine tablets was prepared using optimized formulations of ternary solid dispersed products with excipients by direct compression method (Table 3). All the ingredients in the carbamazepine tablets blends were passed through 60 # separated and mixed in blender (KALVAKA) for 15 min. Tablets were compressed with 10 station rotary machine using 8 mm and 11 mm punch for 220 mg and 420 mg tablet weight respectively at 4 kg/cm^2 pressure.[6,7]

Evaluation of Carbamazepine Tablets Pre-compression

All the optimized formulation of CBZ powder blends was subjected for micrometrics properties using conventional methods. Bulk density and tapped density was determined by using measuring cylinder method. An angle of repose was determined by conventional funnel

method. Hausner's ratios, Carr's index, were determined using the bulk density and tapped density data.[8]

Post-compression

All the optimized formulation of CBZ tablets were subjected to pharmacopeial tests. Tablet thickness, hardness was determined using a vernier caliper and Monsanto hardness tester respectively. Friability, disintegration test and dissolution studies were also performed as per Indian Pharmacopeia (IP) 2014.[8]

Drug Content

Drug Content of CBZ tablet was carried out in both 1.2pH 0.1N HCl and in 6.8 pH phosphate buffer. 10 tablets were selected randomly, weighed and crushed. Powder equivalent to 200mg of carbamazepine was dissolved in 100 ml buffers separately. Serial dilutions were prepared according to Beer`s range. Drug content was analyzed at λ_{max} 285 nm using UV spectrophotometer.[9]

Table 1: Formulation of Binary solid dispersion.

Formulation code	Drug : Polymer ratio	Carbamazepine (mg)	HPMC K-100 (mg)	PVP K-30 (mg)	PEG 6000 (mg)	Methanol (ml)
SD1	1:1	200	200	----	----	20
SD2	1:1	200	----	200	----	20
SD3	1:1	200	----	----	200	20
SD4	1:2	200	400	----	----	20
SD5	1:2	200	----	400	----	20
SD6	1:2	200	----	----	400	20
SD7	1:3	200	600	----	----	20
SD8	1:3	200	----	600	----	20
SD9	1:3	200	----	----	600	20

Table 2: Formulation of Ternary solid dispersion.

Formulation code	Drug: Polymer: Surfactant ratio	Carbamazepine (mg)	HPMC K-100 (mg)	PEG 6000 (mg)	Rhamnolipid 90% (mg)	Poloxamer 407 (mg)	Methanol (ml)
TSD1	1:1	200	200	----	2	----	20
TSD2	1:1	200	200	----	4	----	20
TSD3	1:1	200	200	----	6	----	20
TSD4	1:3	200	----	600	2	----	20
TSD5	1:3	200	----	600	4	----	20
TSD6	1:3	200	----	600	6	----	20
TSD7	1:1	200	200	----	----	5	20
TSD8	1:1	200	200	----	----	10	20
TSD9	1:1	200	200	----	----	15	20
TSD10	1:3	200	----	600	----	5	20
TSD11	1:3	200	----	600	----	10	20
TSD12	1:3	200	----	600	----	15	20

Table 3: Formulation table of carbamazepine tablets using ternary solid disperse product.

INGREDIENTS	FORMULATION CODE	
	OF1	OF
Solid dispersed product equivalent to 100 mg of carbamazepine	400 mg of TSD5	200 mg of TSD2
Cross Carmallose (mg)	5	5
Lactose (mg)	12	12
Magnesium stearate (mg)	2	2
Talc (mg)	1	1

In-vitro Dissolution Study

The *in-vitro* dissolution was performed in acidic and alkaline buffer using USP dissolution apparatus type II at 37±1°C, 50 rpm for 1 hr. Samples were withdrawn from 900 ml dissolution medium and analyzed at λ_{max} 285 nm using UV spectrophotometer and sink condition was maintained.[9]

Stability Studies

Stability studies of optimised formulation was performed at room temperature (25±2°C and 60% RH) and accelerated temperature (40±2°C at RH of 75±5) for 30 days in stability chamber (Kesar Control System). In process stability parameters were performed on 15th day and 30th day for hardness, drug content and drug release studies.[9]

Animal Oral Toxicity Study

Experiment was conducted according to CPSCEA guideline and by approval of animal ethics committee of our institution. Acute oral toxicity study was conducted, according to the test and procedure given in OECD guideline 420. The study is performed using 6 female rats procured from the authorized animal breeding house. As per the limit test mentioned in OECD guideline, oral dose of 2000mg/kg body weight was administered to 1st group of 3 rats and observed for 24 hr for its mortality. Successively 2nd group was administered with the same dose. All animals were observed for 14 days, if mortality is observed the experiment is repeated with lower dose. Food and water intake along with Fecal of animals were observed for 48 hr after administration of dose and also observed up to the end of 15 day.[10]

RESULTS AND DISCUSSION

Compatibility Studies

Carbamazepine FTIR graph showed important functional peaks, carbamazepine was obtained at 3466 cm^{-1} NH stretching, 3068 cm^{-1} CH stretching, C=0 stretching at 1666cm^{-1}, C=C ring stretching at 1602 and 1595. Similar peaks were observed with drug and excipients, indicative of drug and excipients were compatible and stable. Result is observed in Figure 1(a), (b) and (c).

The DSC graphs of Carbamazepine and excipients mixture showed an endothermic peak at 196.2°C and 182.5°C of carbamazepine and biosurfactant respectively. These graphs indicative of compatibility and stability of the physical mixture. Result is observed in Figure 2(a) and (b).

Solubility

The solubility studies of carbamazepine was carried out 0.1N HCl pH 1.2 and 6.8 pH Phosphate buffer. Drug is insoluble in water. The average solubility of Carbamazepine in acidic and alkaline buffer was found to be 0.486 mg/ml and 0.868 mg/ml respectively. The results showed that the drug is highly soluble in 6.8 pH Phosphate buffer.

Evaluation of Solid Dispersed Product

In-vitro Dissolution of Binary and Ternary Solid Dispersion

In-vitro dissolution of binary solid dispersion system consisting of HPMC, PVP and PEG 6000 with different ratio showed the rate of dissolution in the order of PEG 6000< HPMC< PVP. PEG 6000 and drug 1:3 ratio dissolution rate was two folds in accordance with 1:1 ratio. HPMC and drug 1:1 ratio shows maximum rate of dissolution as compared to 1:2 and 1:3 ratio. All ratio of PVP and drug showed not much increase in dissolution rate. From the binary solid dispersion system HPMC and dug 1:1 and PEG 6000 and drug 1:3 ratio was selected for ternary solid dispersion system.

Ternary solid dispersion system of biosurfactant and poloxamer 407 formulation batches consisting of low concentration of biosurfactant and high concentration of poloxamer 407 were prepared. Biosurfactant ternary solid dispersions system *in-vitro* dissolution with HPMC was 38.1% (6mg) and with PEG 6000 rate was 38.69% (4mg). Similarly, with poloxamer 407, HPMC dissolution rate was 24.52% (15mg) and PEG 6000 dissolution rate was 26.87% (15mg). The number of fold increase in the percentage of dissolution rate from binary system to ternary system of HPMC was two folds and for PEG 6000 was 1.2 folds. The increase in % dissolution rate could be the effective penetration and wettability property of biosurfactant in accordance with poloxamer 407. Results are shown in Figure 3(a), (b) and (c).

Formulation of Carbamazepine Tablet

Carbamazepine tablets were prepared by incorporating optimized ternary solid dispersion product (TSD2 and TSD5) with other excipients by direct compression method. Pre-compression and Post-compression parameters were evaluated for the carbamazepine blend powder.

Pre-compression

The micrometric properties of carbamazepine blend powder of OF1 and OF2 for Hausner`s ratio, Compressibility index and angle of repose results were within the acceptable limits. These results revealed that

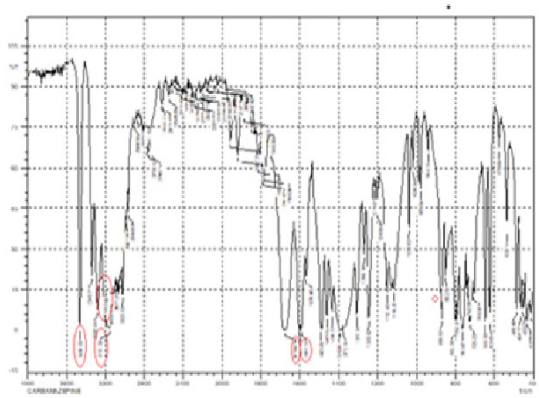

Figure 1a: FT-IR spectrum of pure carbamazepine.

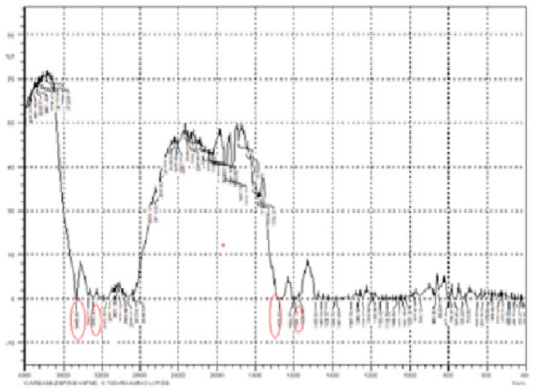

Figure 1c: FT-IR spectra of carbamazepine with HPMC K-100.

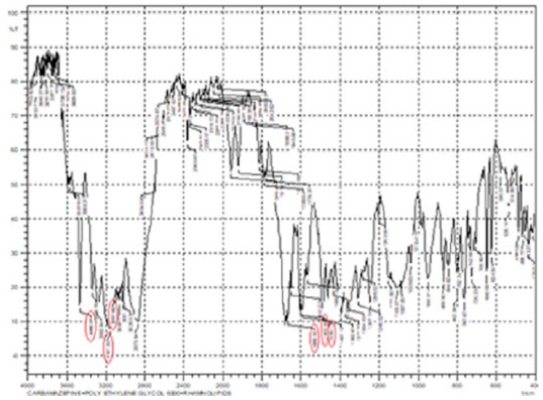

Figure 1b: FT-IR spectra of carbamazepine with PEG 6000.

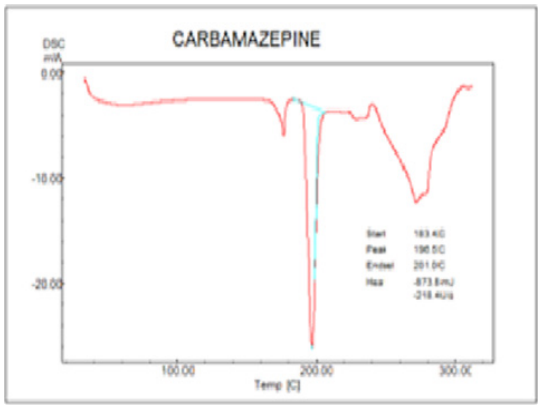

Figure 2a: Thermogram of pure drug Carbamazepine.

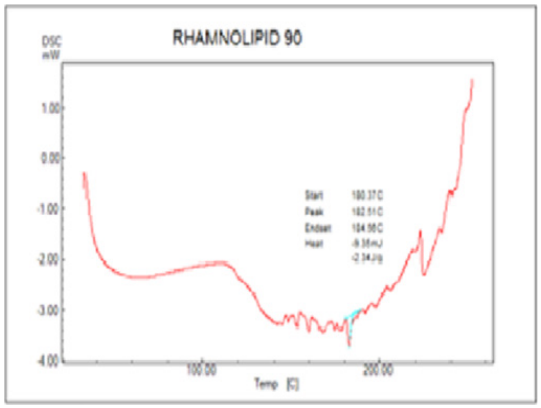

Figure 2b: Thermogram of Rhamnolipids.

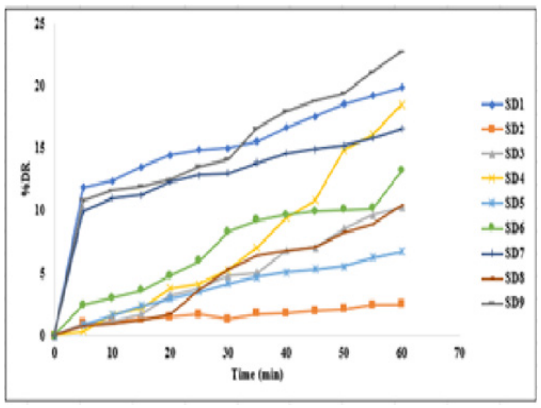

Figure 3a: *In-vitro* drug release of Binary solid dispersion.

carbamazepine powder blends were having free flowing property with good compressibility index. All the results were shown in Table 4.

Post-compression

All Standard Pharmacopeia tests were performed for carbamazepine tablets and the thickness of tablets of OF1 and OF2 was found to be 11.01 mm and 8.1 mm respectively. The hardness of tablets of OF1 and OF2 was found to be 4.0 to 4.22 kg/cm^2. Tablets formulation OF1 and OF2 showed % friability in the range 0.46-0.81 % which was within the limit. All OF1 and OF2 formulations pass weight variation test within the range limit for weight variation found to be 415.2 and 215.1 mg respectively. Drug content results showed uniformity of OF1 and OF2 formulation and was found to be in the range of 90 % to 100 %. Tablet formulations OF1 and OF2 showed disintegration time in the range of 7.0 - 9.0 min. All the results were shown in Table 5.

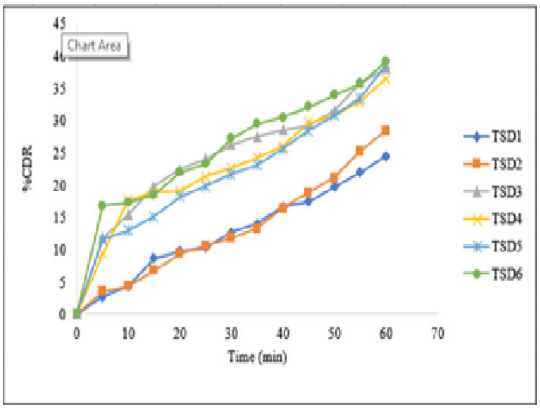

Figure 3b: *In-vitro* drug release of Ternary solid dispersion using Rhamnollpids.

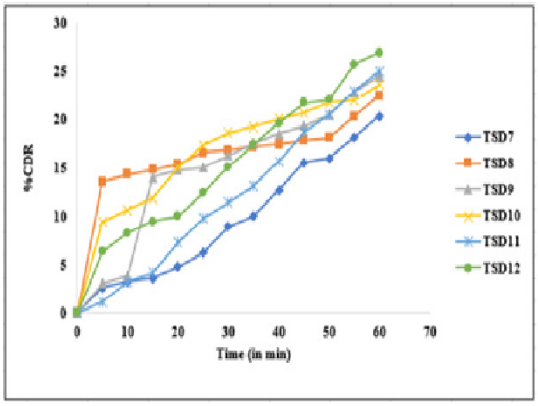

Figure 3c: *In-vitro* drug release of Ternary solid dispersion using Poloxamer.

Table 4: Pre-compression parameters of optimized formulation.

PARAMETERS	FORMULATION CODE OF 1	FORMULATION CODE OF 2
Bulk density (g/ml)*	0.366±0.03	0.197±0.04
Tapped density (g/ml)*	0.415±0.05	0.228±0.05
Carr's Index (%)*	12.77±0.30	15.32±0.43
Hausner's ratio*	1.146±0.01	1.153±0.02
Angle of Repose (ɵ)*	32.82±0.03	34.25±0.04

*Data expressed are average of triplicate (*n*=3±SD)

Table 5: Post-compression parameters of optimized formulation.

PARAMETERS	FORMULATION CODE OF 1	FORMULATION CODE OF 2
Thickness (mm)*	11.01±0.02	8.1±0.04
Diameter (mm)*	4.43±0.20	2.15±0.05
Friability (%)*	0.81±0.40	0.46±0.33
Hardness (kg/cm2)*	4.22±0.28	4.0±0.00
Weight variation (mg)	415.2±0.33	215.1±0.24
Disintegration time*	7±0.22	9±0.11

***Data expressed are average of triplicate (*n*=3±SD)**

In-vitro Dissolution Study

As specified in USP, the dissolution media for carbamazepine tablet is addition of 1% SLS. In our study excluded the SLS and dissolution study was carried out in acidic and alkaline media to mimic biological fluid. The % drug dissolution at 1 hr was for OF1 and OF2 in pH 1.2 buffer 75.14% and 71.26% respectively. In alkaline 6.8 pH phosphate buffer for OF1 and OF2 was 64.33% and 58.96% respectively. The marketed formulation showed 32.98% in acidic pH and 23.13% in 6.8 pH phosphate buffer. The *in-vitro* dissolution result revealed that PEG 1:3 ratio with 4 mg biosurfactant showed maximum drug release in accordance with marketed and OF2 formulation.

Stability Studies

Stability studies at room temperature and accelerated temperature for a 30 days, result revealed that no significant differences were observed for Hardness, Drug content and *in-vitro* drug release for 15 and 30 days at room temperature. In accelerated temperature studies the Hardness, *in-vitro* drug release were deviated from the initial value for 15th and 30th days. The data indicate that the optimum temperature for storage was 25 ± 2°C and 65 ± 5 % RH.

Animal Oral Toxicity Study

These study was performed according to OECD guideline 420, limit test was performed on 6 female rats after IAEC approval. Dose 2000mg/kg body weight was safe without mortality for 14 days. All animals were normal with water and food intake. Oral toxicity study of biosurfactant proved to be safe.

CONCLUSION

Main aim of study was to formulate carbamazepine tablet using ternary solid dispersion product to enhance dissolution rate and bioavailability of poorly soluble drug carbamazepine. Binary and ternary solid dispersion were prepared using water-soluble polymers, biosurfactants and synthesis surfactants and evaluated for % drug release. Ternary formulation with rhamnolipids was compared with poloxamer formulations and resulted that ternary dispersion with biosurfactants showed enhanced dissolution property. Carbamazepine

tablets using PEG and drug (OF1) ternary dispersion revealed good *in-vitro* dissolution results showing high drug release compared with marketed and OF2 formulation. Animal study of biosurfactant proved to be safe at 2000mg/kg bodyweight of rats.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CBZ: Carbamazepine; **DSC:** differential scanning calorimetry; **DT:** dissolution time; **PEG:** polyethylene glycol; **FTIR:** Fourier transmitter infrared spectrophotometer; **HPMC:** Hydroxy propyl methyl cellulose, **TSD:** Ternary solid dispersion, **SD:** Solid dispersion.

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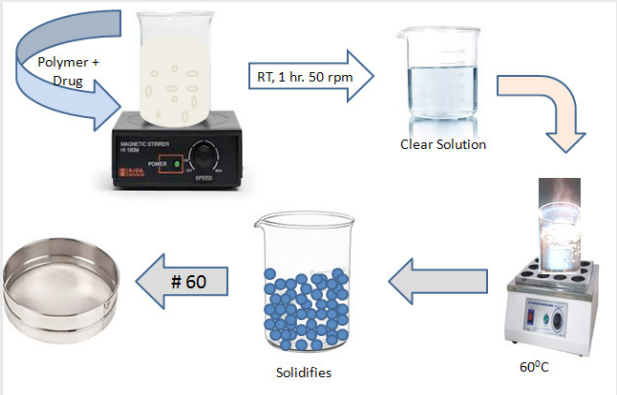
10. Acute oral toxicity study according to OECD guideline 420.

PICTORIAL ABSTRACT



SUMMARY

- Carbamazepine tablet were prepared by incorporation of ternary solid dispersed product along with other excipients by direct compression technique to increase the solubility and bioavailability of drug.
- Binary and ternary solid dispersion were prepared in different ratio using water-soluble polymers, biosurfactants and synthesis surfactants and evaluated for % drug release.
- Ternary formulation with rhamnolipids was compared with poloxamer formulations and resulted that ternary dispersion with biosurfactants showed enhanced dissolution property.
- Animal study of biosurfactant proved to be safe at 2000mg/kg bodyweight of rats.
- Short term stability of the optimized formulation was stable without deviations at room temperature.
- Carbamazepine tablets using PEG and drug (OF1) ternary dispersion revealed good *in-vitro* dissolution results showing high drug release compared with marketed and OF2 formulation.
- Addition of biosurfactant in ternary solid dispersion system proved to be promising excipient in formulation of carbamazepine tablet for enhanced dissolution rate, dose reduction and bioavailability.

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