Formulation Studies of Solid Self-Emulsifying Drug Delivery System of Ivermectin

Vipul P. Patel, Hardik A. Lakkad, Kalpesh Chhotalal Ashara
School of Pharmacy, RK University, Rajkot, Gujarat, India

Correspondence:
Vipul P. Patel, School of Pharmacy, RK University, Rajkot-360020, Gujarat, India.
E-mail: vipul.patel@rku.ac.in
Tel: +919712902310

Received: 15 Oct 2017
Accepted: 22 Feb 2018
Published Online: 05 Apr 2018
Published: 29 Nov 2018

Key words: bioavailability, ivermectin, onchocerciasis, pharmacokinetic, solid self-emulsifying drug delivery system.

Citation: Patel VP, Lakkad HA, Ashara KC. Formulation studies of solid self-emulsifying drug delivery system of ivermectin. Folia Med (Plovdiv) 2018;60(4):580-93. doi: 10.2478/folmed-2018-0024

Background: The suggested dose of ivermectin is 300 μG/kg/day for onchocerciasis but it has low water solubility and poor oral bioavailability.

Aim: To prepare and evaluate a solid lipid-based self-emulsifying drug delivery system of ivermectin.

Materials and methods: Based on supersaturated solubility study, oil, surfactant, and co-surfactant were selected. On the basis of ternary phase diagrams and simplex-lattice design, self-emulsifying, drug delivery formulations had been developed and optimized. Ivermectin-excipients compatibility studies were performed using differential scanning calorimetry and Fourier transform infrared spectroscopy. Solid self-emulsifying drug delivery formulation was formulated from the optimized batch by surface assimilation method and filled into hard gelatin capsules. In vitro release rate and in vivo pharmacokinetic parameters of ivermectin from the capsules were determined. Two-tailed paired t-test/ Dunnett multiple comparison tests were performed for in vivo pharmacokinetic parameter at 95 % of confidence level.

Results: Soybeans oil, tween 80, and span 80 were selected as oil, surfactant, and co-surfactant respectively. The ternary diagrams were shown the maximum area for emulsion in 1:2 surfactant/co-surfactant ratio. The optimized batch had found with 30 mg ivermectin, 6.17 g soybeans oil, 0.30 g tween 80, and 3.50 g span 80. All differential scanning calorimetry and Fourier transform infrared characteristic peaks of the optimized formulation were identical with that of pure ivermectin. The area under the curve of ivermectin from the capsule was about two-fold higher than that of ivermectin suspension.

Conclusions: Solid self-emulsifying drug delivery system was an effective oral solid dosage form to improve the oral bioavailability of ivermectin.

BACKGROUND

The oral route is most convenient for administration of the drug but requires competitive bioavailability for molecule(s).1 Onchocerciasis or river blindness is a disease caused due to Onchocerca volvulus infection, which is the parasitic worm. Symptoms of onchocerciasis include bumps under the skin, blindness, and severe itching. It is the most common cause of blindness.2 Ivermectin (IT) treatment for six months is recommended in onchocerciasis.3 The suggested dose is 300 μG/kg/day for onchocerciasis.4 However, it is a biopharmaceutical classification system (BCS) class II compound (low solubility and high permeability).5 It has poor oral bioavailability (50–60%).6 Therefore, preparation of the oral formulation of IT is quite challenging.

Nowadays, the oral formulation approaches are increased on self-emulsifying drug delivery system (SEDDS) to improve the oral bioavailability of poorly water-soluble drug compounds, especially BCS class II drugs.7 SEEDS are isotropic mixtures of oil(s) with surfactant (S) and co-surfactant (Co-S).8 However, the transportation and handling of SEEDS are difficult as compared to solid dosage form.9 In such conditions, the inert solid carrier could be added to form solid SEDDS (SSEDDS) to maintain its self-emulsifying ability via solidification technique.

AIM

PRIMARY AIM

Formulation. To prepare SSEDDS of IT by solidification technique, using lactose as a solid carrier.
SECONDARY ENDPOINT
Assessment. To compare oral in vivo bioavailability of IT SSEDDS with that of IT suspension.

MATERIALS AND METHODS

MATERIALS
IT was received as a gift sample from Pramukh Pharmaceutical Surendranagar, Gujarat, India. Soybeans oil, methanol, hydrochloric acid (HCl), Whatman paper, and dimethyl formaldehyde (DMF) were purchased from Oxford Laboratory, Mumbai, India. Span 80 and tween 80 were purchased from Loba Chemie Lab., Mumbai, India. IT suspension was purchased from Menarini India Pvt Ltd.

SUPERSATURATED SOLUBILITY STUDY
There was 5 mL of oil, S or Co-S were taken in test tubes (Borosil®) and an excess quantity of IT mixed together, kept for 48 h in Orbital Shaking Incubator (1HB-164, Remi Equipment Ltd., Vasai, India) at 200 rpm. Thereafter, sufficient quantity of supernatant was withdrawn and diluted with respective solvents (methanol and DMF). Absorbance at a specific wavelength (methanol 246 nm and DMF 266 nm) was measured in Double Beam UV visible Spectrophotometer (LT-2900, Labtronics (I) Pvt. Ltd., Ambala, India). Based on absorbance, solubility was measured by using equation derived from calibration plot (y = 0.0277x + 0.046 for methanol and y = 0.0554x + 0.1308 for DMF).10 Solubility study of oil (isopropyl myristate and triacetin) and Co-S (Span 20, PEG-400) were performed using methanol as reference solvent, whereas that of oil (soybeans oil, cod liver oil, castor oil, rose oil), S (tween 80, tween 20), and Co-S (span 80) were performed using DMF as reference solvent.

Preliminary twenty-seven batches (P1–P27) were formulated with S/Co-S ratio of 1:1, 1:2, and 2:1 w/w (Table 1) and evaluated for pH, cloud point (Cp)11, robustness, thermodynamic stability study, and self-emulsification time (SET).

CONSTRUCTION OF TERNARY PHASE DIAGRAM
In ternary phase diagrams, oil was added to S and Co-S mixture and prepared SEDDS in 200 mL 0.1 N HCl. For generating phase diagram at a specific ratio of S/Co-S (i.e. 1:1, 1:2, and 2:1 w/w), 1 mL of prepared bland of S/Co-S was added into 200 mL of 0.1N HCl and evaluated for self-emulsification ability. A clear and homogenous mixture of oil and S/Co-S were formed using magnetic stirrer (2MLH, Remi Equipments Ltd. Mumbai, India) for 5 min at 200 rpm. The resultant mixture was observed visually for phase clarity. The chosen value of oils, as well as S/Co-S mixing ratio, were used to determine boundaries of emulsion domain. To determine the

| S/ Co-S Formula Code | Soybeans Oil (g) | Tween-80 (g) | Span-80 (g) |
|----------------------|------------------|--------------|-------------|
| 1:1 P1               | 1.0              | 4.5          | 4.5         |
| P2                   | 2.0              | 4.0          | 4.0         |
| P3                   | 3.0              | 3.5          | 3.5         |
| P4                   | 4.0              | 3.0          | 3.0         |
| P5                   | 5.0              | 2.5          | 2.5         |
| P6                   | 6.0              | 2.0          | 2.0         |
| P7                   | 7.0              | 1.5          | 1.5         |
| P8                   | 8.0              | 1.0          | 1.0         |
| P9                   | 9.0              | 0.5          | 0.5         |
| 1:2 P10              | 1.00             | 3.00         | 6.00        |
| P11                  | 2.00             | 2.66         | 5.32        |
| P12                  | 3.00             | 2.33         | 4.66        |
| P13                  | 4.00             | 2.00         | 4.00        |
| P14                  | 5.00             | 1.67         | 3.34        |
| P15                  | 6.00             | 1.33         | 2.66        |
| P16                  | 7.00             | 1.00         | 2.00        |
| P17                  | 8.00             | 0.67         | 1.34        |
| P18                  | 9.00             | 0.33         | 0.66        |
| 2:1 P19              | 1.00             | 6.00         | 3.00        |
| P20                  | 2.00             | 5.32         | 2.66        |
| P21                  | 3.00             | 4.66         | 2.33        |
| P22                  | 4.00             | 4.00         | 2.00        |
| P23                  | 5.00             | 3.34         | 1.67        |
| P24                  | 6.00             | 2.66         | 1.33        |
| P25                  | 7.00             | 2.00         | 1.00        |
| P26                  | 8.00             | 1.34         | 0.67        |
| P27                  | 9.00             | 0.66         | 0.33        |

Dose of ivermectin was 30 mg/mL for all batches S/Co-S: Ratio of surfactant / co-surfactant

Unauthenticated | Heruntergeladen 12.02.20 13:57 UTC
effect of IT on emulsion boundary, phase diagrams were also constructed in presence of IT using IT-enriched oil as a hydrophobic component. Phase diagrams were constructed using Prosim ternary diagram software (ProSim, Inc., USA).12

PREPARATION OF LIQUID SEDDS FORMULATIONS
A series of SEDDS formulations were prepared with selected S/Co-S blend and oil by using simplex lattice design. The concentration of oil and S/Co-S ratio were transformed so that minimum concentration corresponds to zero and maximum concentration corresponds to at least one. An accurately weighed IT was placed in a test tube, the added amount of oil, S, and Co-S. Then all components were mixed by magnetic stirrer at 200 rpm until IT was perfectly dissolved. The mixture was kept at room temperature.13

CHARACTERIZATION OF SEDDS FORMULATIONS
All the formulations were evaluated for pH, Cp, robustness, thermodynamic stability study, SET, IT content, dispersibility, and in vitro diffusion study. Robustness to dilution was studied by diluting SEDDS to 50, 100, and 1000 times with 0.1N HCl. The diluted SEDDS were stored for 12 h and determined for any signs of phase separation or IT precipitation.

IN VITRO DIFFUSION STUDY OF SEDDS FORMULATIONS
In vitro, IT diffusion study was performed using modified dialysis technique. One end of pretreated cellulose dialysis tubing (7 cm in length; Nipro Medical India Pvt. Ltd) was tied with IP type I dissolution test apparatus (Electro lab, Mumbai, India) using thread and then 0.1 mL of SEDDS (equivalent to 3 mg IT) was placed in it along with 2 mL of dialyzing medium (0.1N HCl). The opposite end of the tube also secured with thread and was rotated freely in the dissolution vessel containing 200 mL dialyzing medium, maintained at 37±0.5°C and stirred at 50 rpm. The samples were withdrawn at different time intervals of 5 min, 10 min, 15 min, 30 min, 45 min, 60 min, and 75 min.14

OPTIMIZATION OF SEDDS
Using simplex lattice design and Design-Expert 6.0.8 Portable (State-Ease Inc., USA) optimization of the formulations of SEDDS containing IT was performed. The concentrations of oil (X1), S (X2), and Co-S (X3) were chosen as the independent variables. SET, Cp, and cumulative percentage IT release was taken as variable responses (Y).15

IT-EXCIPIENTS COMPATIBILITY STUDY
IT and excipients compatibility studies were performed using differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR):

DSC STUDY
DSC study was performed for pure IT, excipients blends, and optimized formulation using differential scanning calorimeter (D-60, Shimadzu, Japan) in an aluminum cell with a nitrogen atmosphere at a flow rate of 2 g (mL/min).16

FTIR STUDY
IT, excipient blend, and physical mixture of the optimized batch were subjected to FTIR (Shimadzu, Japan) in the scanning range of 350–4600 cm⁻¹ and resolution of 2 cm⁻¹.

PREPARATION OF SOLID SEDDS FORMULATIONS (SSEDDS)
SSEDDS was formulated from liquid SEDDS by surface assimilation to a solid carrier (lactose) in the ratio of 1:3 (e.g. 1 mL SEDDS and 3 g lactose). The surface assimilation method was processed by mixing the liquid formulation and lactose carrier in a laboratory blender (Remi Equipment Ltd., Vasai, India). The resulting SSEDDS was subjected to evaluation of bulk density, tapped density, Hausner’s Ratio, Carr’s index, and angle of repose, then filled directly into hard gelatin capsules (size ‘0’) using manual capsule filling machine (Remi Equipment Ltd., Vasai, India). Weight variation test and disintegration time for capsule formulation of SSEDDS were also evaluated.20

CHARACTERIZATION OF CAPSULE FORMULATION
In vitro dissolution test
The release rate of IT from the capsule was determined using IP dissolution test apparatus type II (basket type, Electro lab, Mumbai, India). SSEDDS capsule was placed in a basket at the beginning of every test. The dissolution test was performed using 900 mL of 0.1N HCl (dissolution media), at 37 ± 0.5°C and 100 rpm speed. There was 3 mL sample withdrawn at different time intervals and replaced with the same volume of fresh dissolution media. The samples were filtered through Whatman paper. The absorbance of these solutions was measured at 246 nm using UV-Visible photometer.21

IN VIVO PHARMACOKINETIC STUDY
Randomized, parallel, experimental study had been
approved for laboratory animal usage for research purposes by the Institutional Animal Ethics Committee (IAEC) of School of Pharmacy, RK University, Rajkot, India (Registration No. 131/PO/RE/S/2007/ CPCESEA) and the guidelines for OECD for testing of chemicals were followed. Male Wistar rats weighing 250±75 g fasted for 10–12 h before the experiments. However, rats were allowed free access to water. Twelve rats were divided into two groups of six rats each. The animals were anesthetized using diethyl ether. In vivo pharmacokinetic parameters of IT were determined after oral administration of IT SEDDS or marketed IT suspension dosage form (0.2 mg/kg of IT) to rats. The blood (100 μL) was collected by the retro-orbital plexus method using capillary at baseline (0 min), at 3 min, 6 min, 12 min, up to 24 h after oral administration of IT formulation. The samples were collected in sodium fluoride/ EDTA tubes (AG Poly Packs Pvt. Ltd., India) and centrifuged at 5000 rpm for 10 min (Cooling centrifuge, Electro lab, Mumbai, India). The plasma was separated by micropipette (40270280, Thermo electron corporation, Finland) and analyzed using double beam UV visible spectrophotometer. All samples were evaluated for T_{max} (time required to release of it into the aqueous phase than marketed formulation (p = 0.0453, q = 3.701) (Table 4). As shown in Fig. 3 inverse relationship exists between SET, t_{90} (time required to release 90% of IT) and C_{p}. However, the quantity of IT diffused was increased. Overlap between t_{90}, SET, and C_{p} (dependent variables) had shown optimized region (Fig. 4). The polynomial mathematical models were prepared as Eqs 1, 2, and 3:

$$t_{90} = -1187.287A - 403.19B - 1533.77C + 5767.21AC + 3494BC + \varepsilon (R^2 = 0.9950; S_v = 0.0101)$$

$$C_{p} = +115.91529A + 0.62603B + 144.42769C + 413.22314AB - 247.93388AC - 413.22314BC + \varepsilon (R^2 = 0.9999; S_v = 0.0001)$$

$$SET = -0.43465A - 3.31594B + 2.04394C + 31.36739AB + 10.29301AC - 10.78137BC + \varepsilon (R^2 = 0.9992; S_v = 0.0469)$$

where, A = soybeans oil, B = tween 80, C = span 80, \(R^2\) = correlation coefficient, \(S_v\) = the significance value of mathematical model, and \(\varepsilon\) = practical error.

The above statistical data indicated that the mathematical model had good accuracy.

One checkpoint cum optimized batch (F8) based on the shared area in overlay contour plot was performed after generating flag chart. DSC study showed that endothermic peaks of
IT + excipients mixture had started with 156.50°C, and the end of 165.29°C (Fig. 5). FTIR study of the optimized batch was exhibited peaks at 3450 cm\(^{-1}\), 1750 cm\(^{-1}\), and 1175 cm\(^{-1}\), which are peaks of the functional group -OH (Phenolic), ester, and ether of IT, respectively (Fig. 6).

The bulk density, tapped density, Hausner’s Ratio, Carr’s index, and angle of repose of SSEEDS had found 0.714±0.002 g/mL, 0.834±0.002 g/mL, 1.161±0.001, 14.29±0.003, and 16.11±0.001\(^{\circ}\), respectively. The weight of capsule was in the range 298±2 mg for weight variation test while disintegrat-
The solubility of ivermectin in different types of oils and surfactants is shown in Table 2. The solubility of ivermectin in coconut was found to be higher than that in cod-liver oil. All data are presented as mean ± SD, n = 5.

## DISCUSSION

All 27-preliminary formulations showed robustness for emulsification after specific dilution (within one min), had a clear or bluish appearance. It ensures the thermodynamic stability of formulations and showing Grade-A type SEDDS (Grade A: Rapidly forming). With respect to physical properties of prepared SEEDS, the choice oil, S, and Co-S were quite appropriate for formulation study.

$C_p$ of prepared SEDDS formulations (F1 - F8) was found to be higher than 60°C. Prepared SEDDS were stable at physiological temperature without risk of phase separation. With respect to the results of physicochemical properties of SEEDS, the study succeeded in the preparation of SEEDS of IT.

All the characteristic peaks of IT and excipients mixture of the optimized formulation were identical with that of pure IT. IT and excipients were compatible with each other. Both DSC measurements and FTIR analysis suggested that IT in the SEEDDS may be in the molecular dispersion state.

Hausner’s Ratio, Carr’s index, and angle of repose of prepared SEEDS were < 1.125, < 15, and < 25 respectively. Physical properties revealed that SEEDDS had free good flow properties. The study was prepared SEEDDS consisted of well-separated particles with a smooth surface.

The higher AUC and $C_{max}$ value of IT was found in SEEDDS formulation than in marketed suspension preparation of IT. AUC of IT from SEEDDS was about two-fold higher than that of IT suspension. The fast rate of diffusion and dissolution may also influence the bioavailability of IT. However, $T_{max}$ value of IT from SEEDDS was not different from those of IT suspension. SEEDDS was increased in the bioavailability of IT compared to the marketed suspension formulation. In respect to the data of $in vivo$ pharmacokinetic study, SEEDDS had preserved the self-emulsification performance of liquid SEDDS.

Six rats were used for the study in two groups to evaluate $in vivo$ pharmacokinetics data. Till date, available studies as simvastatin SEDDS is used six rats in four groups, ketoconazole SEDDS is used four rats in six groups, simvastatin self-micro emulsifying drug delivery system is used three dogs in three groups, and candesartan cilexetil self-nano emulsifying drug delivery system is used six rats in three groups. Moreover, the sample size is not an issue, the more important is effective research design. In respect to the data of the study, the finding was justified the sample size.

In limitations of the study, for example, basic science animal model was applied to human. Only male Wister rats were used. However, sex of animal influences the pharmacokinetics of drugs. There were α-errors observed in results of $in vivo$ pharmacokinetic study because of small sample size. The larges human study is recommended to state the hypothesis strongly.

## CONCLUSION

The experimental formulation study concluded that it was possible to improve the bioavailability of ivermectin using the solid self-emulsifying drug delivery system. Solid self-emulsifying drug delivery system was provided a useful oral solid dosage form for the poorly water-soluble drug, ivermectin.
Figure 2. Ternary phase diagram of self-emulsifying drug delivery system. X: S/Co-S ratio 1:1, Y: S/Co-S ratio 1:2, Z: S/Co-S ratio 2:1. S: Tween 80, Co-S: Span 80. Axis value indicates the fraction of excipient in self-emulsifying drug delivery system. A = soybeans oil, B = tween 80, C = span 80.

ACKNOWLEDGEMENTS
The authors are thankful for all the individuals who took part in the study and other healthcare providers, technicians, and administrative staff who had enabled this work to be carried out. The authors especially thank RK University, Rajkot, Gujarat, India for providing all the necessary facilities to do research. The authors are thankful for the center of excellence department of chemistry, Saurashtra University, Rajkot, Gujarat, India, and Department of Biotechnology, Junagadh Agricultural University, Junagadh, Gujarat, India to provide facilities for DSC study and FTIR study respectively.

The research did not receive any financial support from profitable, non-profitable, or government sector.

CONFLICT OF INTEREST
Author declare that they have no conflict of interest or any the other competing interest that associated with the results or/and discussion reported in the research paper.

REFERENCES
1. Gupta H, Bhandari D, Sharma A. Recent trends in oral drug delivery: A review. Recent Pat Drug Deliv Formul 2009;3(2):162-73.
2. Colebunders R, Mandro M, Mukendi D, et al. Ivermectin treatment in patients with onchocerciasis-associated epilepsy: Protocol of a randomized clinical trial. JMIR Res Protoc 2017;6(8):e137.
3. Gonzalez P, Gonzalez FA, Ueno K. Ivermectin in human medicine, an overview of the current status
Table 3. Formulation and evaluation of self-emulsifying Ivermectin delivery systems

| Evaluation | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8* |
|------------|----|----|----|----|----|----|----|-----|
| Soybeans oil (g) | 6.07 | 3.87 | 3.87 | 4.97 | 4.97 | 3.87 | 4.60 | 6.17 |
| Tween 80 (g) | 0.35 | 2.55 | 0.35 | 1.45 | 0.35 | 1.45 | 1.08 | 0.30 |
| Span 80 (g) | 3.55 | 3.55 | 5.75 | 3.55 | 4.65 | 4.65 | 4.28 | 3.50 |
| S.E.T (sec) | 3.11±0.02 | 3.28±0.06 | 3.41±0.11 | 3.57±0.03 | 3.38±0.07 | 3.21±0.03 | 3.44±0.02 | 3.14±0.8 |
| pH | 6.20±0.21 | 6.10±0.31 | 6.20±0.21 | 6.40±0.11 | 6.30±0.21 | 6.40±0.22 | 6.10±0.12 | 6.20±0.32 |
| Density (g/mL) | 0.95±0.01 | 1.01±0.03 | 0.99±0.25 | 0.96±0.17 | 0.99±0.02 | 0.99±0.03 | 0.99±0.02 | 1±0.25 |
| Cloud point (°C) | 72.01±2.01 | 66.01±3.02 | 70.02±1.01 | 74.01±3.02 | 68.02±2.01 | 63.01±2.02 | 68.02±2.01 | 72.01±2.01 |
| Ivermectin content (%) | 99.06±1.02 | 100.86±0.94 | 100.21±0.32 | 103.08±0.27 | 98.20±0.43 | 100.55±0.57 | 96.93±1.07 | 99.66±0.23 |

No phase separation after specific cycle.
Data are presented as mean ± SD, n = 5.
The dose of ivermectin was 30 mg/mL for all batches.
S.E.T- Self-emulsification time.
*Optimized cum Check Point batch.

Figure 3. Contour plot. X : t₉₀, Y : Cp, Z : SET. t₉₀: time required to release 90% of ivermectin, Cp: cloud point, SET: self-emulsification time. A = soybeans oil, B = tween 80, C = span 80.
Table 4. Diffusion profiles of self-emulsifying drug delivery formulations

| Time (min) | Cumulative percentage ivermectin release | Statistical analysis of F8 and Ivermectin suspension |
|------------|------------------------------------------|-----------------------------------------------------|
|            | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | Ivermectin suspension |
|            |    |    |    |    |    |    |    |    | p-value | q-value |
| 0          | 00±00 | 00±00 | 00±00 | 00±00 | 00±00 | 00±00 | 00±00 | 00±00 |          |         |
| 1          | 54.11±0.51 | 46.87±0.21 | 52.53±0.51 | 26.24±0.41 | 23.12±0.88 | 33.12±0.31 | 18.11±0.59 | 51.76±0.19 | 17.13±1.23 |         |
| 2          | 56.36±0.45 | 49.17±0.15 | 58.82±0.41 | 36.14±0.43 | 27.13±0.71 | 37.13±0.61 | 23.51±0.51 | 54.19±0.25 | 23.15±1.27 |         |
| 3          | 58.61±0.52 | 51.49±0.46 | 69.43±0.39 | 46.41±0.39 | 34.17±0.75 | 42.13±0.45 | 27.12±0.89 | 55.64±0.21 | 33.17±1.19 |         |
| 4          | 60.86±0.53 | 53.81±0.47 | 73.44±0.42 | 55.94±0.33 | 41.18±0.76 | 46.33±0.51 | 29.16±0.93 | 57.11±0.23 | 39.15±1.11 |         |
| 5          | 82.98±0.55 | 99.02±0.47 | 99.52±0.64 | 98.51±0.56 | 47.88±0.93 | 51.08±0.55 | 32.69±0.62 | 77.08±0.27 | 41.12±1.21 |         |
| 10         | 91.25±0.61 | 98.25±0.64 | N/A | 99.02±1.15 | 57.50±0.55 | 62.22±0.47 | 45.68±0.76 | 90.58±0.33 | 65.13±2.25 | 0.0453 | 3.701 |
| 15         | 92.27±0.59 | 97.58±0.70 | N/A | N/A | 64.27±0.70 | 77.08±0.54 | 53.11±0.69 | 94.68±0.78 | 73.12±2.56 |         |
| 30         | 95.30±0.61 | 99.37±0.51 | N/A | N/A | 73.19±0.61 | 82.98±0.72 | 63.07±0.22 | 97.58±0.41 | 81.15±1.19 |         |
| 45         | N/A | N/A | N/A | N/A | 82.98±0.90 | 95.30±0.54 | 88.20±0.47 | 99.37±0.42 | 89.51±2.15 |         |
| 60         | N/A | N/A | N/A | N/A | 88.38±0.66 | N/A | 92.10±0.46 | N/A | 91.13±1.19 |         |
| 75         | N/A | N/A | N/A | N/A | 96.99±0.66 | N/A | 98.01±0.08 | N/A | 99.51±0.48 |         |

All data are presented as mean ± SD, n = 5, N/A: Not applicable.

*Optimized cum Check Point batch.

p < 0.05 and q > 3.359 were considered as significant.
of its clinical applications. Curr Pharm Biotechnol 2012;13(6):1103-9.
4. Shu EN, Okonkwo PO, Ogbodo SO. An improved dosing schedule for ivermectin as a microfilaricidal agent against onchocerciasis. Acta Trop 1997;68(3):269-75.
5. Camargo JA, Sapin A, Nouvel C, et al. Injectable PLA-based in situ forming implants for controlled release of Ivermectin a BCS Class II drug: solvent selection based on physicochemical characterization. Drug Dev Ind Pharm 2013;39(1):146-55.
6. Canga AG, Sahagun Prieto AM, Diez Liebana MJ, et al. The pharmacokinetics and interactions of ivermectin in humans-a mini-review. AAPS J 2008;10(1):42-6.
7. Chaudhari PD, Motewar PP, Sherekar D. Formulation and evaluation of self-emulsifying drug delivery system for BCS Class - II Drug. Der Pharmacia Lettre 2016;8(9):226-36.
8. Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother 2004;58(3):173-82.
9. Mandić J, Zvonar Pobirk A, Vrečer F, et al. Overview of solidification techniques for self-emulsifying drug delivery systems from industrial perspective. Int J Pharm 2017;533(2):335-45.
10. Kang BK, Lee JS. Chon SK, et al. Development of self-micro emulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int J Pharm 2004;274(1-2):65-73.
11. Aboul Fotouh K, Allam AA, El-Badry M, et al. Development and in vitro/in vivo performance of self-nano emulsifying drug delivery systems loaded with candesartan cilexetil. Eur J Pharm Sci 2017;109:503-13.
12. Bhattacharyya A, Bajpai M. Development and oral bioavailability of self-emulsifying formulation of ketoconazole International J Pharm Sci Nanotech 2013;4(5):1858-65.
13. Acharya A, Sanyal SK, Moulik SP. Formation and characterization of a pharmaceutically useful microemulsion derived from isopropyl myristate, polyoxyethylene (4) lauryl ether (Brji-30), isopropyl alcohol and water. Curr Sci 2001 81(4):362-70.
14. Patil P, Patil V, Paradkar A. Formulation of a self-emulsifying system for oral delivery of simvastatin: in vitro and in vivo evaluation. Acta Pharm 2007;57(1):111-22.
15. Bolton S, Bon C. Pharmaceutical statistics - practical and clinical applications. Vol. 135. New York: Marcel Dekker Inc; 2004.
16. Mori NM, Patel P, Sheth NR, et al. Fabrication and characterization of film-forming voriconazole transdermal spray for the treatment of fungal infection Bulletin Facult Pharmacy Cairo Univ 2017;55:41-51.
17. Andonova V, Georgiev G, Dimitrova S, et al. Characterization, in vitro evaluation and stability studies of indomethacin-loaded polyzwitterionic copolymer nanoparticles. Inter J Drug Del Techno 2014;5(3):89-97.
Figure 5 (A, B). Differential Scanning Calorimetry A: Pure ivermectin, endothermic peaks: start: 155.35°C and end: 164.72°C; endothermic heat: -44.14 mJ; -16.98 J/g; sample weight: 2.6 mg. B: The optimized formulation of self-emulsifying ivermectin delivery system, endothermic peaks: start: 156.50°C and end: 165.29°C; endothermic heat: -9.21 mJ; -5.9 J/g; sample weight: 1.56 mg. Cell: Aluminum, Atmosphere: Nitrogen, and flow rate: 20 mL/min.
Figure 6 (A, B). Fourier transforms infrared spectroscopy A: Pure ivermectin. B: The optimized formulation of self-emulsifying ivermectin delivery system. The scanning range: 350–4600 cm\(^{-1}\). Resolution: 2 cm\(^{-1}\). Numbers of scan: 45. Apodization: Happ-Genzel.
### Table 5. *In vivo* pharmacokinetic study parameter

| Parameter               | Ivermectin suspension | Ivermectin SSEDDS | Statistical Analysis |
|-------------------------|-----------------------|-------------------|----------------------|
|                         | Cmax (μG/mL)          | 4312.15±1.12      | 6351.13±1.32         | **p-value** < 0.0001 | **q-value** 3533.5 |
|                         | Tmax (min)            | 901.50±3.27       | 904.50±3.02          | 0.1970               | N/A |
|                         | [AUC]₀ <sup>24</sup> (μG h/mL) | 53337.50±1.88 | 111024.20±3.49 | **p-value** < 0.0001 | **q-value** 43723 |
|                         | [AUC]₀<sup>∞</sup> (μG h/mL) | 92159.33±1.63     | 181150.70±5.92      | **p-value** < 0.0001 | **q-value** 43462 |
| % Relative bioavailability | 100.00±0                   | 196.85±0.51       | < **p-value** 0.0001 | **q-value** 597.94 |

Data are presented as mean ± SD, n = 6.

SSEEDS: Solid self-emulsifying drug delivery system.

*p* < 0.05 and *q* > 2.44 were considered as significant.

N/A: Not applicable

---

18. Tang B, Cheng G, Gu JC, et al. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Discov Today 2008;13(13-14):606-12.

19. Singh I, Kaur B, Juneja P. Preparation and characterization of starch-metal silicate co-precipitates - evaluation as tablet super super disintegrant. Polim Med 2014;44(3):157-66.

20. Huma A, Rizwani GH, Usman M, et al. Drug development of herbomineral capsule (ALG-06) used for hypopigmentation specially in vitiligo. Pak J Pharm Sci 2014;27(5(Special)):1451-7.

21. Pujara ND, Parmar RB. Formulation and evaluation of hard gelatin capsule of losartan potassium. Inventi Rapid: Pharm Tech 2013;2:1-5.

22. The Council concerning the mutual acceptance of data. OECD guideline for the testing of chemicals 2008; 8(OECD TG 452).

23. Bakhle SS, Avari JG. Development and characterization of solid self-emulsifying drug delivery system of cilnidipine. Chem Pharm Bull (Tokyo) 2015;63(6):408-17.

24. Zongwen Gao, Cui F, Xuemei Cao, et al. Local infiltration of the surgical wounds with levobupivacaine, dexibuprofen, and norepinephrine to reduce postoperative pain: a randomized, vehicle-controlled, and preclinical study. Biomed Pharmacother 2017;92:459-67.

25. Rolim LA, Santos FC, Chaves LL, et al. Preformulation study of ivermectin raw material. J Therm Anal Calorim 2015;120(1):807-16.

26. Korat PS, Kapupara PP. Local infiltration of the surgical wound with levobupivacaine, ibuprofen, and epinephrine in postoperative pain: An experimental study. Biomed Pharmacother 2017;96:104-11.
Исследование на предмет разработки твёрдой самоэмульгирующей системы доставки лекарственного средства ивермектина

Випул П. Пател, Хардик А. Лаккад, Калпеш Чоталал Ашара
Фармацевтический факультет, Университет Раджкот, Раджкот, Гуджарат, Индия

Адрес для корреспонденции: Випул П. Пател, Фармацевтический факультет, Университет Раджкот, Раджкот-360020, Гуджарат, Индия
E-mail: vipul.patel@rku.ac.in тел: +919712902310

Дата получения: 15 октября 2017
Дата приемки: 22 февраля 2018
Дата онлайн публикации: 05 апреля 2018
Дата публикации: 29 ноября 2018

Ключевые слова: биологическая наличность, ивермектин, онхоцеркоз, фармакокинетика, твёрдая самоэмульгирующая система доставки лекарственного средства

Образец цитирования: Patel VP, Lakkad HA, Ashara KC. Formulation studies of solid self-emulsifying drug delivery system of ivermectin. Folia Med (Plovdiv) 2018;60(4):580-93.
doi: 10.2478/folmed-2018-0024

Введение: Рекомендуемая доза ивермектина для онхоцеркоза составляет 300 μг / кг / день, но препарат обладает низкой растворимостью в воде и плохой биодоступностью при пероральном приёме.

Цель: Подготовить и проанализировать твёрдую, липидную, самоэмульгирующую систему доставки лекарственного средства ивермектина.

Материалы и методы: На основе исследования сверхрастворимости были селедированы масло, сурфактант и косурфактант. Были разработаны и оптимизированы самоэмульгирующие системы доставки лекарственного средства на основе трёхкомпонентной фазовой диаграммы и симплекс-решётчатых планов. Исследования совместимости ивермектина и эксципиентов проводились с помощью дифференциальной сканирующей калориметрии и инфракрасной спектроскопии с преобразованием Фурье. Была составлена формула твёрдой самоэмульгирующей системы доставки лекарств в качестве оптимизированной партии методом поверхностной ассимиляции и вылита в твёрдые желатиновые капсулы. Были определены скорость освобождения in vitro и in vivo фармакокинетических параметров ивермектина из капсул. Превелись парный двухвыборочный t-тест и тест Дьюнетта для множественного сравнения фармакокинетического параметра in vivo при уровне достоверности 95%.

Результаты: Соевое масло, tween 80 и span 80 были использованы в качестве масла, сурфактант и косурфактант. Трёхкомпонентные диаграммы показывают максимальную площадь эмульсии при соотношении сурфактана / косурфактана 1 : 2. Оптимизированная партия содержала 30 мг ивермектина, 6.17 г соевого масла, 0.30 г tween 80 и 3.50 - span 80. Все пики дифференциальной сканирующей калориметрии и инфракрасной спектроскопии с преобразованием Фурье оптимизированной формулы были идентичны чистой суспензии ивермектина. Площадь под кривой ивермектина из капсул была примерно в два раза выше, чем у суспензии ивермектина.

Выводы: Твёрдая самоэмульгирующаяся система доставки лекарственного средства оказалась эффективной пероральной твёрдой лекарственной формой для улучшения пероральной биодоступности ивермектина.