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Self Double-Emulsifying Drug Delivery System (SDEDDS) for Oral Delivery of Vancomycin Hydrochloride

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ABSTRACT

Water-in-oil-in-water (w/o/w) double emulsions are potential for enhancing oral bioavailability of drugs with high solubility and low permeability, but their industrial application is limited due to the instability. Herein, a novel formulation is developed-a self-double-emulsifying drug delivery systems (SDEDDS) by formulating mixtures of hydrophilic surfactants and water-in-oil (w/o) emulsion. The optimized formulations are stable. SDEDDS can spontaneously emulsify to water-in-oil in-water (w/o/w) double emulsions in the mixed aqueous gastrointestinal environment, with drug encapsulated in the internal water phase of the double emulsions. SDEDDS was employed to improve the oral absorption of Vancomycin Hydrochloride, a peptide-like drug with high solubility and low permeability. The optimized Vancomycin -SDEDDS were found to be stable up to 3 months under 40ºC.

Introduction

Oral administration is the most favourable route of drug delivery for both patients and manufacturers. Nevertheless, for many potential hydrophilic drugs defined as “high solubility low permeability class” or a biopharmaceutical classification system [BCS] class III drugs, gastrointestinal permeation is the rate controlling step in the absorption process. Also the drugs which undergo hepatic first pass effect have low bioavailability which can be improved by absorption and transport through lymphatic system[1]. Many approaches such as absorption enhancers, chemical modifications and pharmaceutical means were used to enhance oral bioavailability of those drugs[2,3]. Among these approaches, water-in-oil-in-water emulsions show great potential for enhancing oral bioavailability of BCS class III drugs, but their industrial application is limited due to instability.

The most important factor affecting the oral absorption of a drug, besides dissolution, is the permeability of the drug across the gastro-intestinal lining. Improving permeability may, therefore, potentially improve the bioavailability of a drug. Transport of hydrophilic drugs across the intestinal epithelium is confined mainly to paracellular pathways. However, the limited surface area and the tight junctions present between the adjacent cells restrict the transport of the drugs and are responsible for the low bioavailability of hydrophilic drugs across the paracellular route. The small oil globules are absorbed through lymphatic system thereby bypass portal circulation and hepatic first pass effect.

Herein, we developed a novel formulation design, self double-emulsifying drug delivery system (SDEDDS), which are the formulated mixtures of water-in-oil (w/o) emulsions and hydrophilic surfactants. Generally w/o/w double emulsions were prepared by a modified two-step emulsification method. SDEDDS changed the process of the second emulsification step, which can self-emulsify to w/o/w double emulsions due to the gastrointestinal peristaltic movements in-vivo instead of artificial emulsification in-vitro. The concept of SEDDS was employed to realize this idea. Self-emulsifying drug delivery systems (SEDDS) are a vital tool with great promise in enhancing the oral bioavailability of poorly water-soluble drugs[7, 8, 9].As isotropic mixtures of drug, oils and surfactants, these systems rapidly disperse in gastrointestinal fluids following their oral administration, yielding micro- or nanoemulsions containing the solubilized drug.[10, 11, 12] Similar to SEDDS, SDEDDS can spontaneously emulsify in the mixed aqueous gastrointestinal environment. But the formed emulsions are water-in-oil-in-water (w/o/w) double emulsions not o/w emulsions, and drugs are encapsulated in the internal water phase of the double emulsions. Compared to conventional thermodynamically unstable double emulsions, SDEDDS are stable formulation systems. In addition, SDEDDS can be filled directly into hard gelatin capsule which are easy to administer and easy to store. The main aim of this study was to develop and characterize SDEDDS formulations. Vancomycin a peptide-like drug was chosen as a model drug of high solubility/low permeability class.[13] Pseudo-ternary phase diagrams was constructed to identify the efficient self-double-emulsification region. The developed formulations were characterized by assessing self double-emulsification performance, viscosity, double emulsions droplet size analysis, microscopy studies, in vitro drug release characteristics and formulation stability studies.

Materials and Methods

Materials

Vancomycin was supplied by the (Alkem Lab, Mumbai). Lecithin was purchased from (Himedia Laboratories Ltd.). Tween 80 (Merck, Mumbai), Span 80 (Shreeji Chemic Ltd.), oleic acid (Loba Chemie Pvt Ltd), soybean oil (Research-Lab Fine Chem Industries) and olive oil (Oxford laboratory Reagent) were obtained. Water was purified by redistillation and filtered through a 0.22 membrane filter before use.

Solubility Studies

An excess amount of Vancomycin (approximately 1 g) was added to each cap vial containing 10ml of the vehicles. After sealing, the mixture was vortexed using a mixer at a maximum speed for 10 min and kept for 48 h at 25ºC in a shaking water bath to facilitate the solubilisation. The samples were

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centrifuged at 3000 rpm for 15 min to remove the undissolved Vancomycin. The supernatant was taken and diluted with ethanol for oil sample and remaining sample with water, quantification of Vancomycin was done by UV spectrophotometer. Initially, the calibration curve of Vancomycin in water and ethanol was plotted.

Construction of pseudo-ternary phase diagrams

Pseudo-ternary phase diagrams were constructed by using the titration method, with the oil phase being replaced by water in- oil (w/o) emulsion. The w/o emulsions was developed by one Step emulsification procedure. Vancomycin was dissolved in distilled water. Then, the Vancomycin aqueous solution was added to the oil phase which consisted with oleic acid, Span 80 and lecithin under moderate magnetic stirring. The chosen w/o emulsion formulation contained 125 g Vancomycin, 20 mg Lecithin, 120 mg Span 80, 330 mg oleic acid, and 80 mg water. A series of mixtures formed with w/o emulsion and aqueous phase were made at certain weight ratios (10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 and 0:10). Each mixture was accurately weighed into glass vials and mixed homogeneously under moderate magnetic stirring at room temperature. Tween 80 was then added into each mixture drop-by-drop by a dropper quantitatively. During the titration process, samples were stirred and observed by optical microscopy. At proper concentration of Tween 80, the structure of double emulsions would appear. The concentration of Tween 80 at which double-emulsions-formation and double emulsions-disappearance transition occurred was obtained by the weight measurements. These values were then used to determine the boundaries of the double emulsion regions, which is corresponding to the selected optimum ratios of combination vehicles for developing Vancomycin-SDEDDS formulations.

Formulation and preparation of SDEDDS

The formulated SDEDDS were mixtures of a hydrophilic surfactant and w/o emulsions. Seven formulations of SDEDDS (F1–F7) containing a fixed proportion of Vancomycin and different amount of phospholipids were prepared[17, 18, 19]. As shown in Table 2, the w/o emulsions were prepared by one step emulsification procedure. Then the w/o emulsions were mixed with Tween 80 using a magnetic stirrer until Vancomycin - SDEDDS was obtained. All the formulations were left for 24 h at room temperature. Hard gelatin capsules (size 00) were manually filled with 715±13mg of each formulation (F1–F7), resulting in each capsule containing 125mg Vancomycin. Vancomycin -SDEDDS capsules were stored in air-tight glass containers at room temperature until required for analysis.

Physical characterization of Sdedds formulations

Weight variation

Twenty capsules were randomly selected from each batch and individually weighed. The average weight and standard deviation of twenty capsules was calculated. The batch passes the test for weight variation if not more than two of the individual capsules weight deviate from the average weight by more than percentage shown in Table below and none deviate by more than twice the percentage shown.

Viscosity analysis of SDEDDS formulations

The rheological measurements of the SDEDDS formulations were performed with a Brookfield viscometer.

Emulsion droplet size analysis

The formulations (F1–F7) droplet size distributions of double emulsions were measured by dynamic light scattering using a Malvern Particle Size Analyzer. SDEDDS were mixed with distilled water (200 ml) and stirred at mild agitation (75 rpm) in a magnetic stirrer for 5min at room temperature, forming the double emulsions. The particle size distribution of the double emulsions was determined.

Drug Content

Ten capsules were weighed accurately and emptied. Content of each capsule equivalent to 125 mg drug was taken and volume was made up to 125 ml with ethanol. From above solution, 1ml was taken and diluted up to 10 ml and absorbance was taken at 281.0 nm. As per USP the drug content of nine capsules must be within ±15% to pass the test.

Visual grading

(A) Denoting a rapidly forming (within 1min) micro emulsion that was clear or slightly bluish in appearance.

(B) Denoting a rapidly forming, slightly less clear emulsion that had a bluish white appearance.

(C) Denoting a bright white emulsion (similar in appearance to milk) that formed within 2 min.

(D) Denoting a dull, gray white emulsion with a slightly oily appearance that was slow to emulsify (longer than 2min).

(E) Denoting a formulation that exhibited either poor or minimal emulsification with large oil droplets present on the surface.

Release from SDEDDS formulations in vitro

The release of drug from the SDEDDS-Capsules was determined using the USP type II dissolution test apparatus. The dissolution test was performed using 900ml of P^H 6.8 phosphate buffer at 37 ± 2^0C and rotational speed of 100 rpm. 5 ml. aliquots were withdrawn at an interval of 1hr. for 8 hrs. The samples were replaced by their equivalent volume of dissolution medium. The samples were analyzed at 281.0 nm by UV spectrophotometer. The % cumulative drug release was calculated using the equation generated from standard curve.

Stability studies

Stability study was performed by storing the ready-to-use Vancomycin-SDEDDS (F5) in the sealed amber glass vials at 25 ^{0}C. The stability was evaluated by monitoring the time-dependent change in appearance, viscosity, self-emulsifying properties and double emulsion droplet size of the SDEDDS formulation within the capsules at 0, 3 month.

Results And Discussion

Solubility studies

The self-double-emulsifying formulations consisted of water, oil, surfactants and drug should be a clear mixture and should have good solvent properties to allow presentation of the drug in the mixture. The solubility results (Table 1) revealed that Vancomycin had high aqueous solubility, and it was therefore solubilized in the internal aqueous core of w/o emulsions, which were the major component of self-double-emulsifying systems. All the oils and surfactants showed poor solubility of the drug. Among the oils tested in this study, Oleic acid was also added because it was reported for its enhanced intestinal absorption of drugs. Span 80 was selected as a hydrophobic surfactant due to its good emulsion-forming ability. Furthermore, Tween 80 was selected as a hydrophilic surfactant for its good compatibility with the w/o emulsions.

Pseudo-ternary phase diagrams

Pseudo-ternary phase diagram was constructed to identify the self-double-emulsifying regions for the selected vehicle (w/o primary emulsion and Tween 80). As shown in Fig. 1, the marked area represents the double emulsion region. It is important to determine this area in order to ensure successful conversation of Vancomycin-SDEDDS to double emulsion by dilution with distilled water. Combined with surfactant different ratios of w/o emulsion to water (from 1:9 to 9:1) spontaneously form water-in-oil-in-water (w/o/w) double emulsions to develop a SDEDDS formulation.

Table 1. Solubility of Vancomycin in various vehicles

Vehicles	Solubility (mg/ml)
Oil	
Soya bean oil	3.54
Olive oil	3.13
Oleic acid	2.82
Castor oil	3.8
Surfactants	
Span 80	9.33
Tween 80	7.33
Aqueous buffer solutions	
P^H 1.2	198
P^H 6.0	107
P^H 6.8	116
P^H 7.4	210
Water	198

Table 2.Composition of formulations F1–F7

S.N.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1.	Vancomycin	125mg	125mg	125mg	125mg	125mg	125mg	125mg
2.	Lecithin	---	05mg	10mg	15mg	20mg	25mg	30mg
3.	Oleic acid	370mg	360mg	350mg	340mg	330mg	320mg	310mg
4.	Span 80	120mg	120mg	120mg	120mg	120mg	120mg	120mg
5.	Water	80mg	80mg	80mg	80mg	80mg	80mg	80mg
6.	Tween 80	40mg	40mg	40mg	40mg	40mg	40mg	40mg

Table 3. Percentage Deviation Allowed Under Weight Variation Test

Percent Deviation Allowed Under Weight Variation Test	
Average Weight of Capsule (X mg)	**Percent Deviation**
$X \leq 80$ mg	10
$80 < X < 250$ mg	7.5
$X \geq 250$ mg	5

Table 4. Evaluation of Formulations (F1 to F4)

Parameters	F1	F2	F3	F4
Appearance	Clear orange yellow liquid			Clear orange yellow semisolid
Viscosity	1530 cp	2105 cp	2855 cp	3590 cp
Globule size (µm)	----	8.69	10.37	12.86
Visual grading	C	C	C	C
Weight variation	735.45 ± 05.85	730.06 ± 07.62	725.21 ± 05.23	720.14 ± 05.68
Content uniformity	97.45 ± 0.25	96.69 ± 0.34	99.32 ± 0.14	98.87 ± 0.24

Table 5. Evaluation of Formulations (F5 to F7)

Parameters	F5	F6	F7
Appearance	Clear orange yellow semisolid		
Viscosity	4330 cp	5005cp	6065cp
Globule size (µm)	13.73	14.20	15.10
Visual grading	C	C	C
Weight variation	715.85±03.56	709.85±04.26	705.85±02.68
Content uniformity	98.58±0.28	97.28±0.21	98.36±0.35

Table 6. Stability study of F5 formulation

Sampling time	Appearance	Viscosity	Visual Grading
0 month	Orange –yellow Liquid	4330cp	C
1 month	Orange –yellow Liquid	4422 cp	C
2 month	Orange –yellow Liquid	4499 cp	C
3 month	Orange –yellow Liquid	4565 cp	C

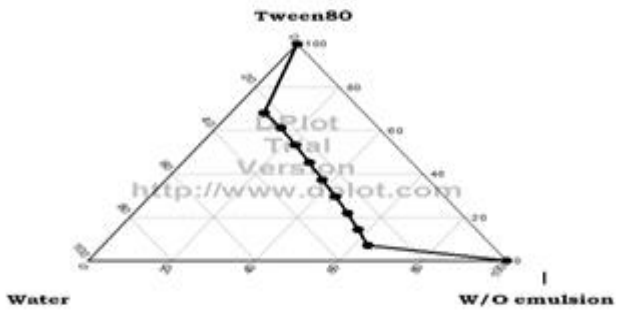

Figure 1. Ternary phase diagram for w/o emulsion, water and Tween 80

Physical properties of different Vancomycin SDEDDS formulations.

Release profiles of Vancomycin from SDEDDS

The in vitro drug release profile for each Formulation is shown in Fig 2. The Graph of % Cumulative drug release v/s Time (hr) was plotted for each Formulation and depicted as Figure2.

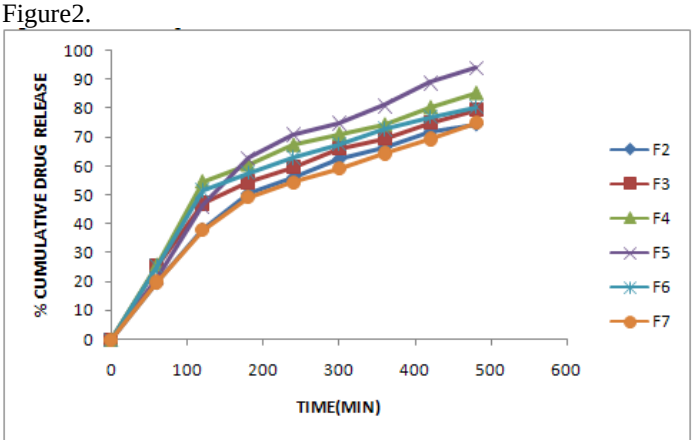

Figure 2. Dissolution profiles of formulations F2 to F7

Stability studies

Stability studies were performed on a optimized formulation F5 for 3 month at 40°C ± 2°C/75% RH ± 5% RH.

Conclusion

The present studies have clearly demonstrated the potential utility of SDEDDS for formulating Vancomycin with sustained release in-vitro thereby improving oral bioavailability in vivo. The optimal formulation of the Vancomycin-SDEDDS (F5) was successfully developed. The SDEDDS readily released the lipid phase to form fine water-in-oil-in-water double emulsions, with a sustained release of Vancomycin. Moreover, the SDEDDS were found to be stable over a period of 3 months under 40˚C. This study illustrated the potential use of novel self-double-emulsifying drug delivery systems for oral delivery drug with high solubility and low permeability.

Following conclusions are obtained from above study:

- The use of lecithin results in increase in viscosity with an increase in concentration.
- The amount of lecithin has significant influence on the globule size of double emulsion.
- Lecithin provides powerful protection to entrapped globule and controls the drug release as barrier.
- Based on the results, F5 was selected as optimum formulation and was successfully developed.

The present study demonstrates the potential use of novel SDEDDS for oral delivery of drugs with high solubility and low permeability.

References

1. Amidon,G.L., H.,Shah,V.P., Crison,J.R., 1995. A theoretical basis for biopharmaceutical classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm.Res.12, 413-420.
2. Miyake, M., Oka, Y., Minami, T., Toguchi, H., Odoni M., Ogawara K., Higaki K., Kimura. T., 2003. Combinatorial use of sodium laurate with taurine or L-glutamine enhances colonic absorption of rebamipide, poorly absorbable antiulcer drug, without any serious histopathological mucosal damages. J. pharm sci. 92, 911-921.
3. Takatsuka, S., Morita, T., Koguchi, A., Horikiri, Y., Yamahara, H., Yoshino, H., 2006. Synergistic absorption enhancement of salmon calcitonin and reversible mucosal injury by applying a mucolytic agent and a non-ionic surfactant. Int. J Pharm. 316, 124-130.
4. Asada, H., Douen, T., Waki, M., Adachi, S., Fujita, T., Yamamoto, A., Muranishi, S., 1995. Absorption characteristics of chemically modified-insulin derivatives with various fatty acids in the small and large intestine. J. Pharm. Sci. 84, 682-687.
5. Koga, k, Takarada, N, Tkada, K, 2010, nano-sized water-in-oil-water emulsion enhances intestinal absorption of calcein, a high solubility and low permeability compound. Eur J Pharm Biopharm. 74, 223-232.
6. Wang, J., Chow, D., Heiati, H., Shen, W. C., 2003. Reversible lipidization for oral delivery of salmon calcitonin. J. Control, Release 88, 369-380.
7. Atef, E., Belmonte, A.A., 2008. Formulation and in vitro and in vivo characterization of a phenytoin self-emulsifying drug delivery system (SEDDS). Eur. J. Pharm. Sci. 35, 257–263.
8. Julianto, T., Yuen, K.H., Noor, A.M., 2000. Improved bioavailability of vitamin E with a self emulsifying formulation. Int. J. Pharm. 200, 53–57.
9. Setthacheewakul, S., Mahattanadul, S., Phadoongsombut, N., Pichayakorn, W., Wiwattanapatapee, R., 2010. Development and evaluation of selfmicroemulsifying liquid and pellet formulations of curcumin, and absorption studies in rats. Eur. J. Pharm. Biopharm.
10. Gursoy, R.N., Benita, S., 2004. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed. Pharmacother. 58, 173–182.
11. Kohli, K., Chopra, S., Dhar, D., Arora, S., Khar, R.K., 2010. Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discov. Today.
12. Singh, B., Bandopadhyay, S., Kapil, R., Singh, R., Katare, O., 2009. Self-emulsifying drug delivery systems (SEDDS): formulation development, characterization, and applications. Crit. Rev. Ther. Drug Carrier Syst. 26, 427–521.
13. Riboldi, P., Gerosa, M., Meroni, P.L., 2009. Pidotimod: a reappraisal. Int. J. Immunopathol. Pharmacol. 22, 255–262.
14. Garti N and Aserin A. Pharmaceutical emulsion, double emulsion, micro emulsion. In microencapsulation and Industrial application. Ed Benita, S. New York, Marcel Dekker 411-534.
15. Fechner, A., Knoth, A., Scherze, I., Muschiolik, G., 2007. Stability and release Properties of double-emulsions stabilised by caseinate–dextran conjugates. Food Hydrocolloid 21, 943–952.
16. Braud L., Paradopoulos K. Visualization of stability and transport in double emulsions. In Aserin A, editor. Multiple emulsions: technology and applications. New jersey: John Wiley & Sons, Inc, 2008 p. 45-65.
17. Zhao, Y., Wang, C., Chow, A.H., Ren, K., Gong, T., Zhang, Z., Zheng, Y., 2010. Self nanoemulsifying drug delivery system (SNEDDS) for oral delivery of Zedoary essential oil:

formulation and bioavailability studies. Int. J. Pharm. 383, 170–17.
18. Yoshida K. et al. Stability of vitamin A in oil-in-water-in-oil types multiple emulsions. Journal of the American Oil Chemists' Society. (1999) 76: 1-6.
19. Onuki, Y., Morishita, M., Takayama, K., 2004. Formulation optimization of water-in-oil in waters multiple emulsions for intestinal insulin delivery. J. Control. Release 97, 91–99.
20. Kavaliunas DR, Frank SG. 1978. Liquid crystal stabilization of multiple emulsions. J Colloid Interface Sci 66 (3): 586 – 588.
21. Doucet O, Ferrero L, Garcia N, Zastrow L. 1998. O/W emulsion and W/O/W multiple emulsions: physical characterization and skin pharmacokinetic comparison in the delivery process of caffeine. Int J Cosmet Sci 20: 283 – 295.
22. Mezzenga R. Equilibrium and non-equilibrium structures in complex food systems. Food Hydrocolloids 21: 674-682.
23. Danner, T. Schubert, H. Coalescence process in emulsion. In food colloids: Fundamentals of formulation. 116-124.
24. Benichou, A., Aserin, T., & Garti, N. (2004). Double emulsions stabilized with hybrids of natural polymers for entrapment and slow release of active matters. Advances in Colloid and Interface Science, 108–109, 29–41.
25. Bandivadekar M.M, Pancholi S.S. Preparation and evaluation of solid self microemulsifying drug delivery system by adsorbent technique to improve dissolution of poorly aqueous soluble drug Ramapril, Int. Res. J. Pharm 2011, 2 (6): 85-90.
26. Dickinson, E and Mc Clements, D, Water-in-oil-water multiple emulsion. In Advances in Food Colloids. Ed. Dickinson, E and Mc Clements, D. J. Cambridge, UK, Blackie academic and professional: 1996, 280-300.
27. United State Pharmacopoeia 2009 Volume III, 3845-3847.