brought to you by **CORE**

Maheshwari et al

Journal of Drug Delivery & Therapeutics. 2019; 9(2):244-249

Available online on 15.03.2019 at http://jddtonline.info



Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-18, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited



Open Open Access

Research Article

"Eco-friendly extraction using solids" - A novel application of mixed solvency concept

R.K. Maheshwari*, Shruti Jain, Anjali Padria, Pawan Mulani, Jaydeep Singh Baghel, Neelesh Maheshwari

Shri G.S. Institute of Technology and Science, 23, Park Road, Indore-452003 (M.P.), India

ABSTRACT

As per the mixed solvency concept (proposed by Dr. R.K. Maheshwari), each and every substance present on the earth has got solubilizing property i.e. all the liquids, gases and solids possess solubilizing power. In the mixed solvency concept, each substance is a solubilizer. We know that all the liquids (matter in liquid state at room temperature) are known as solvents. No solvent is universal solvent. We can say that all the solvents are good solvents for some solutes and bad solvents for other solutes. Similarly, all gases and solids have good solubilizing power for some solutes and bad solvents. Organic solvents have innumerous adverse effects. Such organic solvents should be replaced by other eco-friendly alternative sources. The main objective of this research work is to provide a novel idea to the researchers that solids can also be employed for extraction of active constituents from powders of roots, leaves, seeds, fruits, bark of plants etc. In the present investigation, sesame oil has been extracted from powdered seeds of sesame using solubilizing powers of two solids, thymol and menthol using different methods. Melted thymol (temperature about 50°C), melted menthol (temperature about 45°C) were observed to have very good solubility for sesame oil. Therefore, they were used for extraction of sesame oil. Ethanol was found to be bad solvent for sesame oil. Thymol and menthol improved the solubility of sesame oil in ethanol and helped in extraction. Thymol and menthol are easily removed at about 80°C. Organic solvents are removed from extracts by suitable methods like heating, vacuum distillation etc. These solids (menthol and thymol) are also removable. Also, they can be recollected using suitable methods for recycling purposes.

Keywords: Extraction, mixed solvency concept, sesame oil, menthol, thymol, eutectic liquid, solubilizer

Article Info: Received 31 Jan 2019; Review Completed 04 March 2019; Accepted 09 March 2019; Available online 15 March 2019

Cite this article as:



Maheshwari RK, Jain S, Padria A, Mulani P, Baghel JS, Maheshwari N, "Eco-friendly extraction using solids" - A novel application of mixed solvency concept, Journal of Drug Delivery and Therapeutics. 2019; 9(2):244-249 http://dx.doi.org/10.22270/jddt.v9i2.2409

*Address for Correspondence:

R.K. Maheshwari, Shri G.S. Institute of Technology and Science, 23, Park Road, Indore-452003 (M.P.), India

INTRODUCTION

Some of the common techniques of solubility enhancement include micellar solubilization, complexation, pН modification, salt formation, hydrotropy and cosolvency. A novel technique of solubility enhancement by use of mixed solvency concept has been proposed by Maheshwari1-5. All the substances (whether liquids, gases or solids) have solubilizing power. Innumerable solvent systems may be developed using mixed solvency concept. By application of mixed solvency concept6-19, the drug loading in various pharmaceutical formulations, including NDDS, may be improved and by combining the excipients in appropriate amounts, synergistic solvent actions and additive solvent actions can be obtained and also the problem of toxicity issue due to high concentration of a solvent for desired solubility can be solved. Chandan and Maheshwari¹⁴ utilized mixed solvency concept to improve the drug loading and to reduce the surfactant concentration in SEDDS of candesartan cilexetil. The solubilities of a large number of poorly soluble drugs have been nicely improved utilizing the mixed solvency concept. $^{1\text{-}41}$

The pollution and toxicity caused by most of the organic solvents is a big challenge. The researchers are doing much work to give eco-friendly solutions for this challenge. Organic solvents have innumerous adverse effects caused by single exposure like dermatitis, headache, drowsiness, nausea, eye irritation and long term exposure causes serious effects such as neurological disorders, chronic renal failure, liver damage, necrosis, mutagenesis disorder. They should be replaced by other eco-friendly alternative sources.

The present investigation is an attempt to show that solids can also be wisely used to act as solvent precluding the use of organic solvents. In a separate study, author has attempted soxhelation using phenol as solvent. The vapours of boiling phenol got condensed in extraction chamber to effect the extraction of active constituents from powder of crude drugs. The main objective of the present study is to demonstrate the solvent action of solids.

Maheshwari et al

Maheshwari²⁰ utilized mixed solvency concept to potentiate the solvent character of a weaker solvent. It has been shown that a weaker solvent can be made a strong solvent by incorporation of a solid solubilizer. The solubility of frusemide in ethanol was enhanced about three fold in the presence of 15% w/v niacinamide (a solid solubilizer). Frusemide is sparingly soluble in ethanol and pharmacopoeial method requires dimethyl formamide (a class II organic solvent) for titrimetric analysis of frusemide bulk drug. A solution of niacinamide (15% w/v) in ethanol was successfully employed to carry out titrimetric analysis of frusemide bulk drug, giving an ecofriendly method of analysis because ethanol is a class III organic solvent (relatively safe in comparison to dimethyl formamide.

Various researchers studied the impact of different solvents on sesame oil extraction. They used n-hexane, cyclohexane, benzene, mixture of n-hexane/chloroform, acetic ether, butanol and acetone. Majority of researchers found that nhexane yields higher extraction percentages making it the optimum solvent.

In the present investigation, sesame oil has been extracted from powdered seeds of sesame using solubilizing powers of two solids, thymol and menthol using different methods. Melted thymol (temperature about 50°C), melted menthol (temperature about 45°C) were observed to have very good solubility for sesame oil. Therefore, they were used for extraction of sesame oil. Ethanol was found to be bad solvent for sesame oil. Thymol and menthol improved the solubility of sesame oil in ethanol and helped in extraction. Thymol and menthol are easily removed at about 80°C. Organic solvents are removed from extracts by suitable methods like heating, vacuum distillation etc. These solids (menthol and thymol) are also removable. Also, they can be recollected using suitable methods for recycling purposes.

MATERIALS AND METHODS

Sesame oil and sesame seeds were purchased from local market. Sesame seeds were powdered by means of home mixer. All other chemicals and solvents used were of laboratory grade.

I - Procedure to determine approximate solubility of sesame oil

A) Approximate solubility of sesame oil in melted thymol (temperature about 50°C)

Melting point of thymol is 48°C. One gram of thymol was taken in a test tube and the test tube was dipped in a hot water bath to melt thymol, when a clear, colourless liquid (melted thymol) was obtained, 0.1ml of sesame oil was transferred in test tube and test tube was shaken. Sesame oil got dissolved in melted thymol. Again, 0.1 ml sesame oil was transferred and test tube was shaken. Again, sesame oil was dissolved by melted thymol. Same method was repeated. One ml of sesame oil was easily dissolved by 1 gm melted thymol (at about 50°C). Further addition of sesame oil was stopped. This indicates that even more quantity of sesame oil may be dissolved in 1 gm of melted thymol.

NOTE: During this study, hot water bath was used to keep the thymol in melted condition.

B) Approximate solubility of sesame oil in melted menthol (at about 45°C)

Melting point of menthol is 44°C. One gram of menthol was taken in a test tube and the test tube was dipped in a hot water bath to melt menthol, when a clear, colourless liquid (melted menthol) was obtained, 0.1ml of sesame oil was transferred in test tube and test tube was shaken. Sesame oil

Journal of Drug Delivery & Therapeutics. 2019; 9(2):244-249

got dissolved in melted menthol. Again, 0.1 ml sesame oil was transferred and test tube was shaken. Again, sesame oil was dissolved by melted menthol. Same method was repeated. One ml of sesame oil was easily dissolved by 1 gm melted menthol (at about 45°C). Further addition of sesame oil was stopped. This indicates that even more quantity of sesame oil may be dissolved in 1 gm of melted menthol.

NOTE: During this study, hot water bath was used to keep the menthol in melted condition.

C) Approximate solubility of sesame oil in a solution containing 50% w/v thymol in ethanol-

1 ml of above mentioned solution was kept in a test tube. Sesame oil (0.1 ml) was transferred in it and the test tube was shaken. Oil got dissolved in solution. Further, 0.1 ml sesame oil was transferred and the test tube was shaken. Again, oil got dissolved. Same procedure was repeated. It was found that 1ml solution was able to dissolve 1.4 ml of sesame oil (1.5 ml sesame oil caused turbidity). This study indicated that sesame oil has very good solubility in the mentioned solution.

D) Approximate solubility of sesame oil in a solution containing 50% w/v menthol in ethanol-

1 ml of above mentioned solution was kept in a test tube. Sesame oil (0.1 ml) was transferred in it and the test tube was shaken. Oil got dissolved in solution. Further, 0.1 ml sesame oil was transferred and the test tube was shaken. Again, oil got dissolved. Same procedure was repeated. It was found that 1ml solution was able to dissolve 0.8 ml of sesame oil (0.9 ml sesame oil caused turbidity). This study indicated that sesame oil has quite good solubility in the mentioned solution.

E) Approximate solubility of sesame oil in a solution containing 25% w/v thymol and 25% menthol in ethanol (25 T 25M E) –

1 ml of above mentioned solution was kept in a test tube. Sesame oil (0.1 ml) was transferred in it and the test tube was shaken. Oil got dissolved in solution. Further, 0.1 ml sesame oil was transferred and the test tube was shaken. Again, oil got dissolved. Same procedure was repeated. It was found that 1ml solution was able to dissolve 0.9 ml of sesame oil (1.0 ml sesame oil caused turbidity). This study indicated that sesame oil has quite good solubility in the mentioned solution.

F) Approximate solubility of sesame oil in a eutectic liquid of menthol and thymol in 1:1 ratio (M:T-1:1)

Thymol (25 gm) and 25 gm menthol were triturated with the help of pestle and mortar to get clear colorless liquid (eutectic liquid). This eutectic liquid (M:T-1:1) was kept in a bottle for further study. One ml of M:T-1:1 was kept in a test tube. Sesame oil (0.1 ml) was transferred in it and the test tube was shaken. Oil got dissolved in it. Further, 0.1 ml sesame oil was transferred and the test tube was shaken. Again, oil got dissolved. Same procedure was repeated. It was found that 1ml of this eutectic liquid was able to dissolve 1 ml of sesame oil. This study indicated that sesame oil has very good solubility in M:T-1:1.

II - Studies to see the removability of solids by heating

(a) Thymol – One gm of thymol was kept on a weighed s.s. plate (stainless steel plate) and exposed to about 80°C in oven. It was found that all thymol was removed within 45 minutes.

- (b) Menthol One gm of menthol was kept on a weighed s.s. plate and exposed to about 80°C in oven. It was found that all menthol was removed within 30 minutes.
- (c) Removability of thymol from an oily solution containing thymol in sesame oil - Weight of a small s.s. plate was noted. On this plate, an oily solution containing 1 gm thymol and 1 gm sesame oil is transferred and again the gross weight is noted. Plate is exposed to about 80°C in an oven. All menthol is removed in about 30 minutes. NOTE : Sesame oil remains on the plate. It does not vaporize at this temperature (about 80°C). Thus, we can employ melted thymol (temperature about 50°C) for extraction of sesame oil from powdered sesame seeds.
- (d) Removability of menthol from an oily solution containing menthol in sesame oil - Weight of a small s.s. plate was noted. On this plate, an oily solution containing 1 gm menthol and 1 gm sesame oil is transferred and again the gross weight is noted. Plate is exposed to about 80°C in an oven. All menthol is removed in about 30 minutes. NOTE : Sesame oil remains on the plate. It does not vaporize at this temperature (about 80°C). Thus, we can employ melted menthol (temperature about 45°C) for extraction of sesame oil from powdered sesame seeds.
- (e) Removability of thymol &/or menthol from other oily solutions (using s.s. plate method)

Same procedure (like method c) was used to observe the removability of thymol &/or menthol from following oily solutions.

- (i) Oily solution containing 1 ml of 50% w/v thymol in ethanol solution and one gram sesame oil.
- (ii) Oily solution containing 1 ml of 50% w/v menthol in ethanol solution and 0.8 gm sesame oil.
- (iii) Oily solution containing 1ml of eutectic liquid (menthol:Thymol,1:1) and 1 gram of sesame oil.
- (iv) Oily solution containing 1 ml of an ethanolic solution containing 25% w/v thymol and 25% w/v menthol and 0.9 gram of sesame oil.

In all above studies it was found that thymol &/or menthol are completely removed within 30-60 minutes at about 80°C in oven. Nearly 100% recovery of sesame oil was found on the s.s. plates. The smell of thymol and/or menthol was absent in the oil present on the s.s. plates. These studies indicate that there is complete removal of thymol and menthol. Tests to detect the presence of menthol and thymol traces in the extracted sesame oil were not performed in the present research work.

III – Extraction Methods

E 1) Extraction of sesame oil from powdered sesame seeds with melted thymol (temperature about 50°C) -

Powdered sesame seeds (5gm) were transferred in a 250 ml capacity beaker. Then, 15 gm thymol was added. Beaker was kept on hot water bath to melt the thymol (M.P. 48°C). When thymol got melted, the beaker was shaken for 30 minutes. During this time, the thymol was kept in melted condition with the help of hot water bath. During these 30 minutes shaking, melted thymol acted as solvent and dissolved the sesame oil of powdered sesame seeds. After 30 minutes shaking, the contents were strained through a muslin cloth. Strained liquid was transferred on a weighed s.s. plate. This plate was kept in oven for removal of thymol at about 80°C. About one hour was required to get a constant weight of plate together with extracted oil.

Journal of Drug Delivery & Therapeutics. 2019; 9(2):244-249

Yield of sesame oil was found to be 1.88 gm.

(Obtained oil contained some pulp material also, in addition to sesame oil).

E 2) Extraction of sesame oil from powdered sesame seeds with a solution containing 50% w/v thymol in ethanol (50 T E)

Powdered sesame seeds (3 gm) were transferred in a beaker of 250 ml capacity. Then, 9 ml of 50 T E was transferred. The beaker was shaken for 30 minutes for extraction of sesame oil from powdered sesame seeds. After 30 minutes shaking, the contents were transferred in centrifuge tubes and centrifugation was carried out for 3 minutes at 12000 rpm using Eppendorf Centrifuge 5415. Then, decanted clear liquid was kept on weighed s.s. plate and kept in an oven at about 80°C for removal of thymol and ethanol. Constant weight of s.s. plate together with extracted oil was obtained in about 1 hour.

0.66 gm sesame oil was left on this s.s. plate. Pulp was nearly absent in this case.

E 3) Extraction of sesame oil from powdered sesame seeds with melted menthol (temperature about 45 $^{\circ}\text{C}$) -

Powdered sesame seeds (3gm) were transferred in a 250 ml capacity beaker. Then, 12 gm menthol was added. Beaker was kept on hot water bath to melt the menthol (M.P. 44°C). When menthol got melted, the beaker was shaken for 30 minutes. During this time, the menthol was kept in melted condition with the help of hot water bath. During these 30 minutes shaking, melted menthol acted as solvent and dissolved the sesame oil of powdered sesame seeds. After 30 minutes shaking, the contents were strained through a muslin cloth. Strained liquid was transferred on a weighed s.s. plate. This plate was kept in oven for removal of menthol at about 80°C. About one hour was required to get a constant weight of s.s. plate together with extracted oil.

Yield of sesame oil was found to be 1.40 gm.

(Obtained oil contained some pulp material also, in addition to sesame oil).

E 4) Extraction of sesame oil from powdered sesame seeds with a solution containing 50% w/v menthol in ethanol (50 ME)

Powdered sesame seeds (3 gm) were transferred in a beaker of 250 ml capacity. Then, 9 ml of 50 M E was transferred. The beaker was shaken for 30 minutes for extraction of sesame oil from powdered sesame seeds. After 30 minutes shaking, the contents were transferred in centrifuge tubes and centrifugation was carried out for 3 minutes at 12000 rpm using Eppendorf Centrifuge 5415. Then, decanted clear liquid was kept on weighed s.s. plate and kept in an oven at about 80°C for removal of menthol and ethanol. Constant weight of s.s. plate together with extracted oil was obtained in about 1 hour.

0.81 gm sesame oil was left on this s.s. plate. Pulp was nearly absent in this case.

E 5) Extraction of sesame oil from powdered sesame seeds with a solution containing 25% w/v thymol and 25% w/v menthol in ethanol (25 T 25 M E)

Powdered sesame seeds (3 gm) were transferred in a beaker of 250 ml capacity. Then, 9 ml of 25 T 25 M E was transferred. The beaker was shaken for 30 minutes for extraction of sesame oil from powdered sesame seeds. After 30 minutes shaking, the contents were transferred in centrifuge tubes and centrifugation was carried out for 3

Maheshwari et al

minutes at 12000 rpm using Eppendorf Centrifuge 5415. Then, decanted clear liquid was kept on weighed s.s. plate and kept in an oven at about 80°C for removal of thymol, menthol and ethanol. Constant weight of s.s. plate together with extracted oil was obtained in about 1 hour.

1.10 gm sesame oil was left on this s.s. plate. Very little traces of pulp were present.

E 6) Extraction of sesame oil from powdered sesame seeds with a eutectic liquid of menthol and thymol in 1:1 ratio (M:T - 1:1)

Powdered sesame seeds (3 gm) were transferred in a beaker of 250 ml capacity. Then, 9 ml of M:T – 1:1 was transferred. The beaker was shaken for 30 minutes for extraction of sesame oil from powdered sesame seeds. After 30 minutes shaking, the contents were transferred in centrifuge tubes and centrifugation was carried out for 3 minutes at 12000 rpm using Eppendorf Centrifuge 5415. Then, decanted clear liquid was kept on weighed s.s. plate and kept in an oven at about 80°C for removal of thymol and menthol. Constant weight of s.s. plate together with extracted oil was obtained in about 1 hour.

0.80 gm sesame oil was left on this s.s. plate. Pulp was nearly absent.

E 7) Extraction of sesame oil from powdered sesame seeds with hexane

Powdered sesame seeds (5gm) were transferred in a bottle of 100 ml capacity. Then, 15 ml of hexane was transferred. The bottle was shaken for 30 minutes for extraction of sesame oil from powdered sesame seeds. After 30 minutes shaking, the contents were filtered to get extract of sesame oil. Then, extract was kept on weighed s s plate and kept in an oven at about 80°C for removal of hexane. Constant weight of s.s. plate together with extracted oil was obtained in about 30 minutes.

0.97 gm sesame oil was left on this s.s. plate. Very minute traces of pulp were present.

Journal of Drug Delivery & Therapeutics. 2019; 9(2):244-249

RESULT AND DISCUSSION

Table I gives approximate solubility of sesame oil in different solvents. Melted thymol (temperature about 50°C) shows very good solubility of sesame oil. More than 1 ml of sesame oil gets dissolved in 1gm melted thymol i.e. more than 50% solubility. Similarly, more than 1 ml of sesame oil gets dissolved in 1 gm melted menthol (temperature 45°C), hence more than 50% solubility. One ml of 50% w/v thymol solution in ethanol dissolved 1.4 ml of sesame oil (about 58% w/v solubility). One ml of 50% w/v menthol solution in ethanol dissolved 0.8 ml of sesame oil (about 44% solubility). One ml of an ethanolic solution containing 25% thymol and 25% menthol dissolved 0.9 ml of sesame oil (about 47% solubility). One ml of eutectic liquid menthol:thymol - 1:1 dissolves more than 1 ml of sesame oil i.e. more than 50% solubility. All solvent systems show significant solubilities for sesame oil. Removability studies show that thymol, menthol and ethanol can easily be removed at about 80°C within 1 hour. Based on all above considerations, it was thought worthwhile to employ these solvent systems for extraction of sesame oil from powdered sesame seeds.

Table II shows the results of percent yield of extracted sesame oil from powdered sesame seeds employing different extraction methods. The observed values of percent yield of sesame oil are approximate values because some oil is left with marc, some oil adheres to vessels, some oil adheres to cloth during straining and some oil adheres to the filter paper. Certain improvements in such extraction methods require -

(1) To see the effect of time of extraction.

(2) To see the effect of multiple extraction (two times or three times etc.).

(3) To see the effect of different ratios of amounts of solvent and powdered sesame seeds.

(4) To see the effect of different particle sizes of powdered sesame seeds.

S. N.	Solvent	Approximate solubility
1	Melted thymol (at about 50°C)	More than 1 ml sesame oil in 1 gm melted thymol
2	Melted menthol (at about 45°C)	More than 1 ml sesame oil in 1 gm melted menthol
3	50 % w/v Thymol in ethanol	1.4 ml sesame oil in 1 ml of 50 %w/v thymol in ethanol
4	50 % w/v Menthol in ethanol	0.8 ml of sesame oil in 1 ml of 50 % w/v menthol in ethanol
5	25%w/v thymol 25 %w/v menthol in ethanol	0.9 ml of sesame oil in 1 ml of 25%w/v thymol 25%w/v menthol
		in ethanol
6	Eutectic liquid M:T - 1:1	More than 1 ml of sesame oil in 1 ml of M:T - 1:1

Table - I Results of approximate solubility studies of sesame oil

Table - II Results of extraction studies using different techniques

S. No.	Solvent	Yield of sesame oil
1	Melted thymol	37.6 %w/w (with little pulp)
2	50%w/v Thymol in ethanol	22.0%w/w (pulp was nearly absent)
3	Melted menthol	33.3 %w/w (with little pulp)
4	50%w/v Menthol in ethanol	27.0 %w/w (pulp was nearly absent)
5	25%w/v Menthol 25%w/v Thymol in ethanol	36.6 %w/w (with traces of pulp)
6	Eutectic liquid M : T - 1:1	26.6%w/w (pulp was nearly absent)
7	Hexane	32.3 %w/w (with traces of pulp)

Journal of Drug Delivery & Therapeutics. 2019; 9(2):244-249

Maheshwari et al

CONCLUSION

Present research work nicely explains that the solubilizing properties of solids can be employed for extraction of active constituents from various powders of plant materials giving ecofriendly methods. The use of toxic, pollution causing organic solvents can be minimized /avoided. In the present study the solvent power of ethanol was improved using solids (menthol and thymol), so that ethanol (a safer class III solvent) could be used to extract sesame oil. Literature survey revealed that hexane (a harmful solvent) is used with ethanol to extract sesame oil (ethanol is a weaker solvent for sesame oil). Ethanol is a class III organic solvents. Class III organic solvents are better than class II organic solvents (like chloroform, methanol etc.) from the point of view of safety, pollution etc.

Sometimes because of poor solubility of active constituents in ethanol, we are unable to use ethanol for extraction purpose and we use harmful organic solvents. Ethanol can be made a strong solvent using menthol, thymol etc. as reported in this research work. Thus, there is bright future of solubilizing properties of solids for extraction purposes. Such work should be promoted by the researchers for ecofriendly extractions of active constituents.

Extraction with hexane was performed for comparison purpose only. Hexane is largely employed for extraction of various oils. Also, in some of the extraction methods, little amount of pulp was found together with extracted oil. Keeping in mind, all these facts, it can be said that there is requirement of further refinement in the procedures of extraction. However, this study is model study to show that solids can nicely be employed for extraction of active constitutent from herbal sources. Solids also possess solubilizing properties. So, many solids can be employed for extraction of active constituents. Literature survey shows that various harmful solvents (hexane, cyclohexane, chloroform, acetic ether) have been employed for extraction of seasame oil. Beauty of this research work is that traces of thymol or menthol left in the extracted oil may not be harmful. During removal of thymol and/or menthol from extracted portion, thymol and menthol can be collected employing vaccum distillation, so that they can be recycled. However, distillation shall require exposure to a much higher temperature.

REFERENCES

- Maheshwari RK. "Mixed-solvency approach"- Boon for solubilization of poorly soluble drugs. Asian Journal of Pharmaceutics 2010; Jan-March: 60-63.
- 2. Maheshwari RK. Solubilization of ibuprofen by mixed solvency approach. The Indian Pharmacist 2009; 8(87): 81-84.
- Maheshwari RK. "Mixed-solvency" A novel concept for solubilization of poorly water-soluble drugs. Delving J. Tech. Eng. Sci. 2009; 1(1):39-43.
- 4. Rajesh Kumar Maheshwari, "Solid as solvent", Novel spectrophotometric analysis of satranidazole tablets using phenol as solvent. The Indian Pharmacist 2014, XII:37-40.
- 5. Maheshwari RK. "Solid as solvent"-Novel spectrophotometric analysis of tinidazole tablets using melted phenol as solvent. Asian Journal of Pharmaceutical Research, 2015; 5(1):21-24.
- 6. Maheshwari RK, Shilpkar R. Formulation development and evaluation of injection of poorly soluble drug using mixed solvency concept. International Journal of Pharma and Biosciences 2012; 3(I):179-189.
- Maheshwari RK, Rajagopalan R. Formulation and evaluation of paracetamol syrup made by mixed-solvency concept. Der Pharmacia Lettre 2012; 4(1): 170-174.
- Soni LK, Solanki SS, Maheshwari RK. Solubilization of poorly water soluble drug using mixed solvency approach for aqueous injection. British Journal of Pharmaceutical Research 2014; 4(5):549-568

- 9. Maheshwari RK, Karawande VU, Application of novel concept of mixed solvency in the design and development of floating microspheres of furosemide. International journal of Pharmacy and Pharmaceutical Sciences 2013; 15:167-195.
- 10. Maheshwari RK, Chaklan N, Singh S, Novel pharmaceutical application of mixed solvency concept for development of solid dispersions of piroxicam, European Journal of Biomedical and Pharmaceutical Sciences 2015; 1(3):578-591.
- 11. Agrawal A, Maheshwari RK. Formulation development and evaluation of in situ nasal gel of poorly water soluble drug using mixed solvency concept. Asian Journal of Pharmaceutics 2011; 5(3):131-140.
- Prashant B, Rawat S, Mahajan YY, Galgatte UC, Maheshwari RK. Formulation development and evaluation of aqueous injection of poorly soluble drug made by novel application of mixed solvency concept. International Journal of Drug Delivery 2013; 2:152-166.
- Maheshwari Y, Mishra DK, Mahajan SC, Maheshwari P, Maheshwari RK, Jain J. Novel pharmaceutical application of mixed solvency in the formulation development of syrups (liquid oral solutions) of poorly water-soluble drugs. International Journal of Pharmacy 2013; 3(4):753-758.
- Chandna C, Maheshwari RK. Mixed solvency concept in reducing surfactant concentration of self emulsifying drug delivery systems of candesartan cilexetil using D-optimal mixture design. Asian Journal of Pharmaceutics 2013; April-June: 83-91.
- 15. Maheshwari RK, Rajagopalan R. Formulation and evaluation of tinidazole syrup made by mixed-solvency concept. Der Pharmacia Lettre 2011; 3(6):266-271.
- Love Kumar Soni, Shailendra Singh Solanki, Rajesh Kumar Maheshwari. Studies on mixed solvency concept in formulation development of oral solution (syrup) of poorly water soluble drug, Journal of Harmonized Research in Pharmacy 2015; 4(4):305-315.
- 17. Maheshwari RK, Jain R, George P. Formulation development and evaluation of controlled release tablets of lamotrigine
- using mixed solvency concept, Bulletin of Pharmaceutical Research 2015; 5(1):14-19.
- 18. Maheshwari RK and Jain S, Formulation and development of high concentration diclofenac sodium injection using mixed solvency concept and its evaluation, International Journal of Advanced Pharmaceutics 2016; 6(2):78-84.
- 19. Padiyar A, Maheshwari RK, Novel dry injection for reconstitution of aspirin using solid solubilizers, Journal of Drug Delivery and Therapeutics 2017; 7(7):44-45.
- 20. Maheshwari RK. Potentiation of solvent character by mixed solvency concept: A novel concept of solubilization. Journal of Pharmacy Research 2010; 3(2):411-413.
- 21. Maheshwari RK, Upadhyay N, Jain J, Patani M, Mathuria KC. New spectrophotometric estimation of naproxen tablet formulation employing mixed solvency concept (at 331 nm). International Journal of Pharmacy and Technology 2011; 3(4):3618-3623.
- 22. Maheshwari RK, Gupta S, Gharia A, Garg SK, Shilpkar R. Simple eco-friendly spectrophotometric estimation of tinidazole tablets by application of mixed-solvency technique. Bulletin of Pharmaceutical Research 2011; 1(1):22-25.
- Bhawsar N, Maheshwari RK, Ansari A, Saktawat Y. New spectrophotometric estimation of gatifloxacin in the tablets using mixed solvency approach. International Journal of Pharmaceutical Science 2011; 2(2):270-274.
- 24. Maheshwari RK, Upadhyay N, Jain J, Patani M, Pandey R. New spectrophotometric analysis of gatifloxacin tablets utilizing mixed solvency concept (at 288 nm). Der Pharmacia Lettre 2012; 4(1):1-4.
- 25. Sreegiriprasad B, Gupta VRM, Devanna N, Ramadevi M, Vishnuvarethan rao G. Mixed Solvency Concept: A promising tool to enhance solubility of poorly soluble drug aceclofenac. International Journal of Pharmaceutical Chemical and Biological Sciences 2012; 3:338-342.
- 26. Vijayranga G, Deveswaran R, Bharath S, Basavraj BV, Madhavan V. Development of an analytical method for spectrophotometric estimation of ketoprofen using mixed solvency approach. International Journal of Pharmaceutical Sciences and Research 2012; 4:1053-1056.
- 27. Maheshwari RK. "Solid as solvent"-Novel spectrophotometric analysis of frusemide tablets using phenol as solvent. Bulletin of Pharmaceutical Research 2014; 4(2):104-107.

Maheshwari et al

- Maheshwari RK, Putliwala M, Padiyar A. Novel approach for spectrophotometric estimation of naproxen in tablet dosage form using solids (eutectic liquid of phenol and niacinamide) as solubilizing agent (mixed solvency concept). Asian Journal of Pharmaceutical Research, 2015; 5(1):25-28
- Maheshwari RK, Kori S, Sonkesariya N, Joshi A, "Solid as solvent"- Spectrophotometric estimation of satranidazole tablets using solids (eutectic liquid of phenol and lignocaine hydrochloride) as solubilizing agents (mixed solvency concept), World Journal of Pharmaceutical Research 2017; 6(3):628-634.
- 30. Maheshwari RK, Maheshwari N, Maheshwari N, Sahu T, Jain J, "Solid as solvent"- Novel spectrophotometric analytical method for quantitative estimation of gatifloxacin tablets using solids (eutectic liquid of phenol and lignocaine hydrochloride) as solubilizing agents (mixed solvency concept), European Journal of Biomedical and Pharmaceutical Sciences 2017; 4(8):644-648.
- 31. Jain S, Maheshwari RK, Nema RK, Singhvi I, Development and validation of simple uv-spectrophotometric method of quantitation of ondansatron hydrochloride in solid dosage formulations using hydrotropic solubilization technique, International Journal of Pharmaceutical Sciences and Drug Research 2017; 9(5):210-213.
- 32. Maheshwari RK, Dahima R, "Solid as solvent"- Novel spectrophotometric analytical technique for quantitative estimation of tinidazole in tablets using solids (eutectic liquid of phenol and lignocaine hydrochloride) as solubilizing agents (mixed solvency concept), Journal of Drug Delivery and Therapeutics 2017; 7(3):127-130.
- 33. Jain S, Maheshwari RK, Nema RK, Singhvi I, Development and validation of simple uv-spectrophotometric method of quantitation of nifedipine in solid dosage formulations using mixed solvency concept, World Journal of Pharmaceutical Research 2017; 6(13):2014-1021.
- 34. Jain S, Maheshwari RK, Nema RK, Singhvi I, Development and validation of simple uv-spectrophotometric method of

Journal of Drug Delivery & Therapeutics. 2019; 9(2):244-249

quantitation of diazepam in bulk drug and solid dosage formulation using mixed solvency concept, International Journal of Current Pharmaceutical Research 2017; 9(6):15-17.

- 35. Jain S, Maheshwari RK, Nema RK, Singhvi I, Development and validation of simple uv-spectrophotometric method of quantitation of domperidone in solid dosage formulations using using mixed solvency concept, Research and Reviews: A Journal of Drug Design and Discovery 2017; 4(2):19-23.
- Journal of Drug Design and Discovery 2017; 4(2):19-23.
 36. Maheshwari RK, Sharma R, "Solid as solvent"- Novel spectrophotometric analysis of saranidazole tablets using solids (eutectic liquid of phenol and metformin hydrochloride) as solubilizing agents (mixed solvency concept), The Pharma Innovation Journal 2016; 5(2):42-43.
- 37. Jain S, Maheshwari RK, Nema RK, Singhvi I, Simultaneous estimation of ofloxacin and tinidazole in solid dosage form by uv-spectrophotometry using mixed solvency concept, European Journal of Pharmaceutical and Medical Research, 2017;4(12):413-418.
- 38. Jain S, Maheshwari RK, Nema RK, Singhvi I, Development and validation of simple uv-spectrophotometric method of quantitation of domperidone in solid dosage formulations using using mixed solvency concept, European Journal of Biomedical and Pharmaceutical Sciences 2017;4(12):548-551.
- Jain S, Maheshwari RK, Nema RK, Singhvi I, Development and validation of simple uv-spectrophotometric method of quantitation of indomethacin in solid dosage formulation using using mixed solvency concept, The Pharma Innovation Journal 2017; 6(12):453-456.
- 40. Jain S, Maheshwari RK, Nema RK, Singhvi I, Simultaneous estimation of norfloxacin and tinidazole in solid dosage form by uv-spectrophotometry using mixed solvency concept, World Journal of Pharmaceutical and Medical Research, 2018; 4(1):112-117.
- 41. Jain S, Maheshwari RK, Nema RK, Singhvi I, New spectrophotometric estimation frusemide in the tablets using mixed solvency concept, International Journal of Current Advanced Research 2017; 6(12):8510-8513.