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FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF STABLE DOLASETRON HCL NANOSUSPENSION FOR IMPROVED DISSOLUTION

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ABSTRACT

The present work was formulation development and invitro evaluation of stable Dolasetron HCL nanosuspension. Four formulations were formulated with different stablizers and surfactants. Out of four formulations, the formulation with the stabilizer and surfactant that resulted in low value of particle size and PDI were selected for further optimization. (T1- PS 287.3 and PDI 0.385). The obtained particle size, PDI and zeta potential was found to be 228.2nm, 0.376 and - 7.8mv respectively. Invitro dissolution studies revealed that formulation F5 has uplifted drug release of 92.5% and 98.9% on 40 minutes at pH 1.2 and pH 6.8 respectively. The drug release kinetics optimized nanosuspension at pH 7.4 revealed that the formulations undergone First order / anamolus / non-fickian diffusion drug release. So it is evident that formulating into nanosuspension results in improved stability, solubility and rapid drug release.

KEYWORDS: Nanosuspension, different stablizers and surfactants, kinetics, non-fickian diffusion.

INTRODUCTION

Nanoparticulate systems provide enhanced absorption due to the slower elimination rate of these particle.[1] Currently more than 40% of new chemical entities are reported to be lipophilic compounds and one-third of drugs recognized by United States Pharmacopeia are poorly soluble. During the process of drug exploration and investigation, more and more new drug candidates have been found to be insoluble or poorly soluble in aqueous medium or organic solvent. Poor solubility may trigger issues, such as poor bioavailability due to uncontrollable precipitation and an erratic absorption profile. Bioavailability refers to the percentage of drug that has been incorporated into circulation of human body. Therefore, developing new formulating strategies for drug molecules with poor solubility to attain an adequate bioavailability has become a challenge for the scientific and industrial professionals. Several methods have been developed, such as complexation by surfactants or cyclodextrins, solid dispersions, Solubilization using co-solvents, salt formation, screening of soluble drug analogs or prodrugs and application of permeation enhancers, oily solutions, and surfactant dispersions. Even though that methods have achieved some reasonable success, their limitation, such as a large amount of additives that may induce stability and toxicity issues. Therefore, a unique strategy is urgently needed that can resolve the formulation-related challenges so as to improve their clinical efficacy and maximally optimize the pharmaco- economics.[2]

The nanosuspension drug delivery system (DDS) was firstly reported in 1994 and a lot of research efforts were devoted to it so as to generate a general formulation for the poorly soluble drugs. Nanosuspension is a colloidal dispersion of submicron drug particles. A pharmaceutical nanosuspension is usually defined as very finely dispersed and biphasic colloid containing solid drug particles of a size less than 1 μm. The suspension contains no matrix material and is stabilized by surfactants and polymers. It is prepared via suitable routes as DDS for the application of oral topical, parenteral, ocular, and pulmonary administration. Nanosuspensions with the drug particle reduced to nano-size exhibit excellent advantages. Reducing the particle size can greatly increase the solubility, thus improving the bioavailability. Additionally, there are other distinguished advantages, such as easy formulation, ease of scale-up, narrow size distribution of drug particle, controllable drug quantity, and little batch-to-batch variation. Moreover, this strategy can be generally applied to drugs with poor solubility in both aqueous and nonaqueous media. The nanosuspension DDS also makes it possible for the drug to be applied as a liquid dosage form or transformed into solid dosage form, such as tablet or capsule. Therefore, the drug can be administrated via oral, pulmonary, ocular, dermal, and intravenous routes. A decent number of nanosuspension DDS products have been marketed.[3]

PREPARATION OF LIQUID NANOSUSPENSION DDS

Liquid nanosuspension DDS is a liquid colloidal dispersion of crystalline or amorphous drug nanoparticles with average size below 1000 nm, stabilizers and liquid dissolution medium. Stabi-lizers are polymer surfactants utilized to maintain the stability of a nanosuspension. The liquid dissolution medium is water, aqueous solution, non aqueous solution, or organic solvent. A variety of factors, such as the crystalline structure and particle size of the drug nanoparticle can affect its saturation solubility.[14] Other factors, such as dissolution medium and temperature also play a role. According to the Kelvin and the Ostwald-Freundlich equations, the saturation solubility increases with the decrease of particle size when the size of the drug particles falls below the size of 1 μm. Drug particle size reduction also results in an increase in surface area, thus accelerating the rate of dissolution and improving the bioavailability. Many fabrication techniques have been developed to prepare the liquid nanosuspension DDS by research laboratories and pharmaceutical professionals.

Those methods are generally classified into three categories as:
(1) Top-down technology,
(2) Bottom-up technology, and
(3) Combination technol- ogy.

Other preparation techniques, such as supercritical fluid technology, emulsification-solvent evaporation method, and melt emulsification method exhibit some excellent advantages and will be discussed as well in the following section.[4]
Surfactant
Salt formation
pH adjustment
Hydrotrophy
Solid dispersion.

Dolasetron is an antinauseant and antiemetic agent indicated for the prevention of nausea and vomiting associated with moderately-emetogenic cancer chemotherapy and for the prevention of postoperative nausea and vomiting. Dolasetron is a highly specific and selective serotonin 5-HT3 receptor antagonist. This drug is not shown to have activity at other known serotonin receptors, and has low affinity for dopamine receptors. Chemically called as: [(3S,7R)-10-oxo-8-azatricyclo[5.3.1.03,8]undecan-5-yl] 1H-indole-3-carboxylate

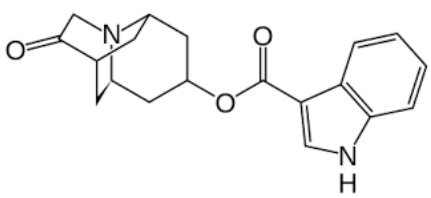

Figure 1: Chemical Structure Of Dolasetron Hydrochloride.

Materials used

Dolasetron Hydrochloride collected as a free sample from Medopharm, Hosur, Poloxamer- 188 from Sigma Aldrich, Kolliphor RH 40 from BASF Chemicals, Tween- 80 and PEG 4000 from Loba chem.

METHODOLOGY

PREFORMUALTION STUDIES[8]

Preformulation studies involve physical, chemical and biological characterization of new drug substances in order to develop stable, safe and effective dosage form. Preformulation testing encompasses all studies enacted on a drug compound in order to produce useful information for subsequent formulation of a stable and bio-pharmaceutically suitable drug dosage form.

Melting Point[9]

Determination of λ max[8]

Standard Curve[9]

FT-IR Studies (Drug- Polymer Compatibility)[10]

Drug polymer compatibility was determined by ATR plate method using Fourier Transform Infrared Spectrophotometer. The samples were prepared by using ATR plate method and it was scanned between 400-4000 cm^{-1}.

Preparation of Dolasetron Hydrochloride Nanosuspension[11]

Dolasetron hydrochloride nanosupension was prepared by Nano precipitation method. Aqueous solutions of stabilizers was prepared by dissolving poloxamer 188, tween 80, PEG 4000 and kolliphor RH 40 in water using magnetic stirrer. HPMC was added to aqueous phase as crystal growth inhibitors. Dolasetron hydrochloride was suspended in the stabilizer solution. The organic phase containing drug solution was slowly injected into aqueous phase using syringe. Then the mixture was subjected to probe sonication for 15 min.

Characterization of Dolasetron hydrochloride Nanosuspension[12-14]

Particle size

The average particle size of prepared Nanosuspension was determined using dynamic light scattering using Malvern Zetasizer (Nano ZS90, Malvern instruments) at 25°C. The samples were kept in polystyrene cuvette and the readings were measured at a fixed angle.

Polydispersity index (PDI)

Mean particle size and Polydispersity index (PDI) of prepared Nanosuspension were obtained using Malvern Zetasizer (Nano ZS90, Malvern instruments). After suitable dilution, prepared nanosuspension was added to the sample cell and determination was carried out. PDI values give idea about uniformity of size distribution.

Zeta potential

The zeta potential of prepared Nanosuspension was measured using Malvern Zetasizer (Nano ZS90, Malvern instruments) at 25°C. The samples were measured by zeta dip cell kept in polystyrene cuvette.

Drug Content[14-16]

Drug content was determined by ultra centrifugation technique**.** Nanosuspension was dissolved in centrifuge tube containing 2 ml of distilled water. The solution was centrifuged at 12,000 rpm for 10 minutes. It was filtered and supernatant solution was analyzed using UV visible spectrophotometer at 248nm.

TDC = Vol. total / Vol. Aliquot drug × amount in aliquot × 100

% TDC = TDC / TA×100

Dissolution study: dialysis sac method

4–5 cm long portion of the dialysis tubing was made into a dialysis sac by folding and tying up one end of the tubing with thread. The sac was filled with 2 ml of the oral marketed solution of Dolasetron hydrochloride and formulated nanosuspension of Dolasetron hydrochloride. The sacs were suspended in the glass beakers containing 500 ml pH 0.1 and the glass beaker was stirred on magnetic stirred at 100 rpm. A 1 ml sample was taken until 2 h at the time interval of 5, 10, 15, 30, 45, 60, 90, and 120 min. An equal amount of fresh dissolution media was added after the withdrawal of each sample.

***In-vitro* Drug release kinetic**[16]

The release kinetic models for the *in-vitro* drug release profile were established using DD solver software. The release data of the optimized formulations were run in the software for various kinetic models. The model showing the best fit with respect to the regression coefficient (R2) was chosen to determine the release pattern of the drug from the Nanosuspension.

RESULTS AND DISCUSSION

Melting Point

Melting point of dolasetron hydrochloride was determined by capillary tube method and it was found to be 180°C respectively, which confirms the purity of the drug.

Determination of absorption maxima

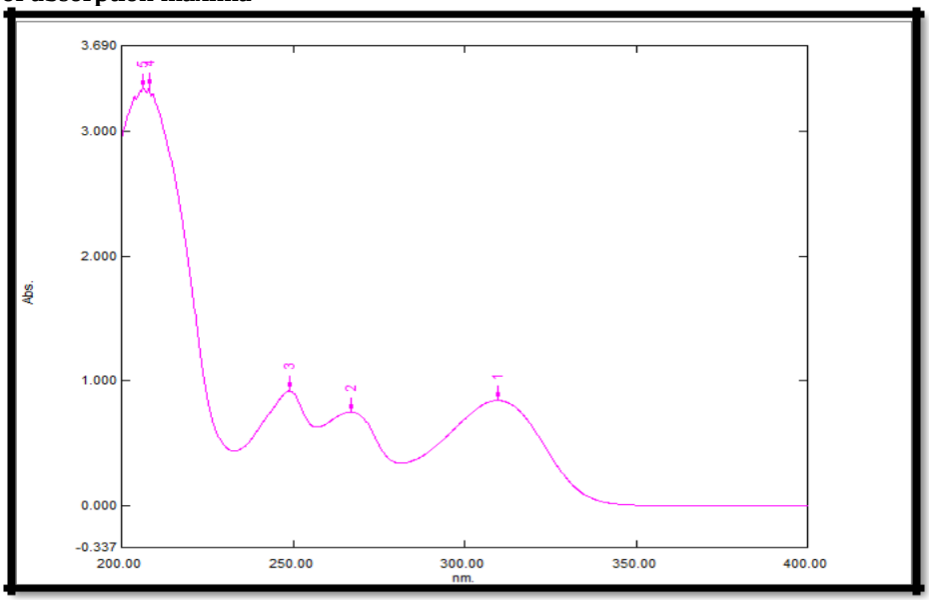

Figure 2: λ max of Dolasetron hydrochloride.

The stock solution containing 1.0 µg/ml was taken for detection of absorption maxima. 1ml of the stock solution was analyzed in the range of 200-400nm in UV spectroscopy. The maximum absorption was found at λ max 249nm.

CALIBRATION CURVE OF DOL HCL

Table 2: Calibration curve of Dolasetron hydrochloride.

S.No	Concentration (µg/ml)	Absorbance at pH 1.2	Absorbance at pH 7.4
1	0	0	0
2.	0.2	0.17	0.182
3.	0.4	0.355	0.357
4.	0.6	0.562	0.542
5.	0.8	0.728	0.754
6.	1	0.919	0.928

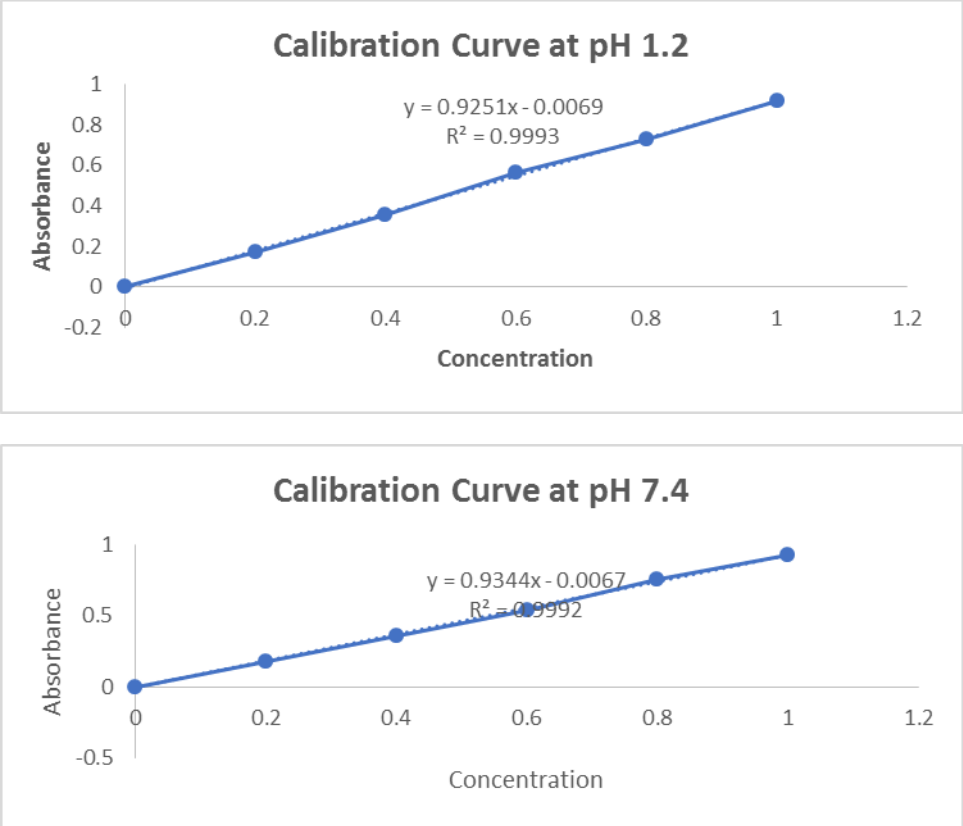

Figure 3: Calibration graph of Dolasetron hydrochloride at pH 1.2 and pH 7.4.

Standard graph was constructed with concentration range of 0.2 to 1.0 µg/ml. The absorbance was determined corresponding to their concentration were shown in Table 5. & Fig 7. Correlation coefficient r^2 was found to be 0.9985 with a linear plot which indicates that DOL Hcl obey Beer lamberts law at the concentration range of 0.2 to 1.0 µg/ml.

Compatibility study

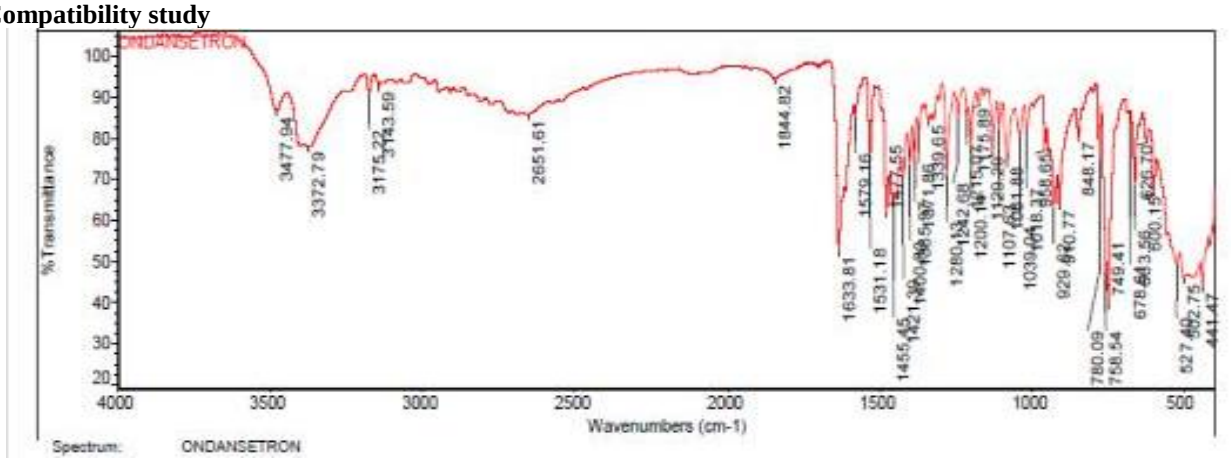

Figure 4: FT-IR spectrum of Dolasetron hydrochloride.

Formulation of DOL HCl nanosuspension

DOL HCl nanosuspension were formulated using Tween 80 (2.5%), Polaxamer (0.5%), PVP (5%) and Kolliphor RH 40 (1%) as stabilizers with HPMC (1.25%) as crystal growth inhibitors using probe sonicator at sonication time of 15 mins. The formulated suspension were investigated for its particle size, zeta potential and PDI to identify ideal stabilizer.

Drug Content

Table 3: Drug content of formulations T1 to T4.

S. No	Formulation Code	Drug Content (AVG±SD)
1	T1	93.63±1.6226
2	T2	89.63±1.9561
3	T3	93.70±1.3856
4	T4	87.86±1.8013

Particle size and Zeta Potential

Table 4: Particle size and Zeta potential of formulations T1 to T4.

S.No	Formulation Code	Particle Size	PDI	Zeta Potential
1	T1	287.3	0.385	-7.82
2	T2	523.1	0.756	-10.7
3	T3	1163	1	-13.1
4	T4	844.9	0.993	-17.4

The results of particle size, PDI and zeta potential for the formulations T1 to T4. The particle size of formulation T1 containing Tween 80 (2.5%) was 287.3nm, PDI 0.385 and zeta potential -7.82 were found to be significant. Whereas the other formulations were not within the optimum range.

Particle size, PDI and Zeta potential

The optimized batch showed the particle size 267.3 nm with PDI of 0.326. The drug content was found to be 87.71. The low value of PDI suggested that narrow particle size distribution and homogeneity of the formulation.

The zeta potential value confirms the physical stability of the formulation. Physical stability of the nanosuspension solely depends on the electrostatic repulsion force called zeta potential. Zeta potential depends on the ion nature of the polymer, surfactant and drug. HPMC and Tween 80 are non ionic in nature. A low level concentration of HPMC and high level concentration of surfactant.

Table 5: Cumulative dissolution data of test formulation, market formulation and pure drug at pH 1.2.

S.No	Time in Mins	Pure drug	Optimized Nanosuspension
1	0	0±0	0±0
2	5	4.8±0.56	40.2±0.59
3	10	13.98±0.67	74.9±0.87
4	20	18.56±0.32	96.5±0.73
5	30	26.87±0.78	95.4±0.69
6	40	37.65±0.59	92.3±0.49

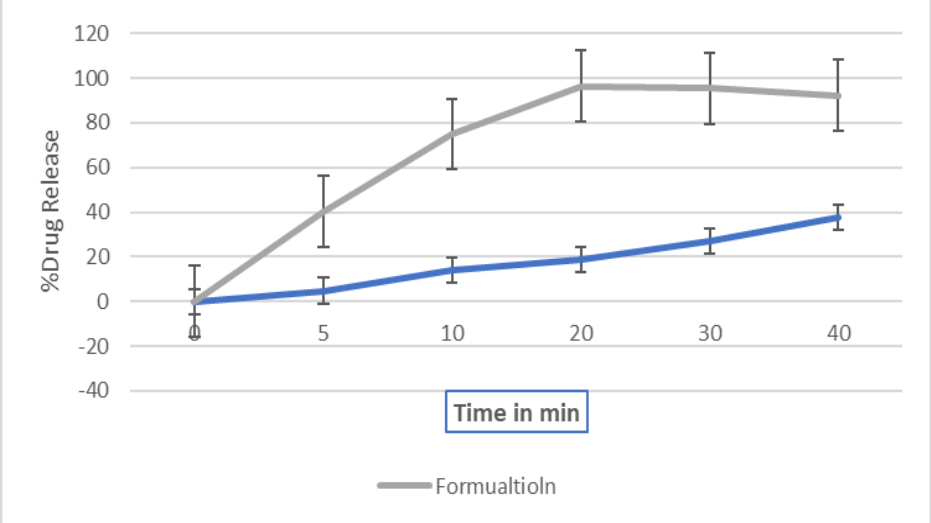

Figure 5: Comparison of dissolution study of test formulation and pure drug at pH 1.2.

In-vitro Drug release kinetics

The release kinetic modeling was performed using the parameters that provide the closest fit between experimental observations and the nonlinear function. The best fits model was selected as per the obtained correlation coefficient (r^2) values. The model, which gives highest^2 value, is considered as the best fit of release data. According to the obtained^2 values, the release data is well fitted to the first order kinetic model for release at pH 7.4 and Hixson croxwell model at pH 1.2. Based on the obtained *n* values for optimized nanosuspension at pH 7.4 the formulations undergone First order / anamolus / non-fickian diffusion drug release. The drug was released in a time dependent manner by diffusion and swelling.

SUMMARY AND CONCLUSION

The present study demonstrated that Dolasetron HCl loaded nanosuspension were successfully developed. Four formulations were formulated with different stablizers and surfactants. Out of four formulations, the formulation with the stabilizer and surfactant that

resulted in low value of particle size and PDI were selected for further optimization. (T1- PS 287.3 and PDI 0.385). The obtained particle size, PDI and zeta potential was found to be 228.2nm, 0.376 and - 7.8mv respectively. Invitro dissolution studies revealed that formulation F5 has uplifted drug release of 92.5% and 98.9% on 40 minutes at pH 1.2 and pH 6.8 respectively. The drug release kinetics optimized nanosuspension at pH 7.4 revealed that the formulations undergone First order / anamolus / non-fickian diffusion drug release. so it is evident that formulating into nanosuspension results in improved stability, solubility and rapid drug release.

CONCLUSION

It may be concluded that the nanosuspension of poorly soluble drugs such as Dolasetron are easy to prepare and represent a promising novel approach for oral drug delivery. It is evident that the obtained results of *invitro* dissolution studies of the formulation T1 shows improved solubility and rapid drug release. Consequently, nanosuspension represent a promising alternative delivery system for improving the physiochemical properties of BCS class II drugs.

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