

DEVELOPMENT OF MUCOADHESIVE DELIVERY OF CHLORZOXAZONE POLYETHYLENE GLYCOL SOLID DISPERSION

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ABSTRACT

Objective: Chlorzoxazone (CLZ) is centrally acting skeletal muscle relaxant. It is insoluble in water, so employed for the formation of solid dispersions (SD) as a means to enhance the dissolution rate, and carrier selected was polyethylene glycol 6000 (PEG 6000).

Methods: The SDs were prepared by different methods and characterized by *in vitro* drug release, drug content, fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry, powder X-ray diffraction. All the SD showed dissolution improvement compare to pure drug. These techniques revealed distinct loss of drug crystallinity in the formulation accounting for enhancement in dissolution rate. The SD methods showing best *in vitro* drug release profile were selected in the further development of mucoadhesive buccal patches. A buccal patch has been developed using two mucoadhesive polymers, i.e. hydroxyl propyl methyl cellulose K4M and carbopol 974. The patches were evaluated for the physicochemical, mechanical and drug release characteristics. The optimized patches showed good mechanical and physicochemical properties to withstand the environment of the oral cavity. The *in-vitro* permeation study showed that patches could deliver drug to the oral mucosa for a period of 8 hrs.

Results: The results indicate that suitable bioadhesive buccal patches with good permeability could be prepared. The batches FH4 and FC4 showed 81.95% and 79.97% permeated through goat mucosa membrane in 8 hrs. The physicochemical interactions were investigated by FTIR, showed no any evidence of interactions and were present in an unchanged state. The stability study for SD and buccal patch carried out revealed that were stable for a period of 3-month.

Conclusion: Phase-solubility studies indicate significantly increase in solubility. The optimized buccal patches showed good mechanical and physicochemical properties to withstand environment of the oral cavity.

Keywords: Solid dispersions, Chlorzoxazone, Dissolution studies, Buccal patch, *In vitro* permeation studies.

INTRODUCTION

Poorly water-soluble drugs (BCS Class II drugs) often show low bioavailability when administered orally, because the absorption of the drugs in the gastrointestinal-tract can usually be a rate-limiting step. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. An improvement of the dissolution rates of water-insoluble drugs remains one of the most challenging and important tasks of drug development as the enhanced dissolution rates can increase drug oral bioavailability [1-3].

Chemically, Chlorzoxazone (CLZ) is 5-chloro-3H-benzooxazol-2-one, which belongs to a skeletal muscle relaxant (centrally acting) class. It has half-life of 1.1 hrs and dose is 250 mg. It is soluble in methanol, ethanol and isopropanol; freely soluble in aq. solutions of alkali hydroxides and slightly soluble in water. Although CLZ is rapidly absorbed after oral administration, it is critical to improve the dissolution rate of CLZ to enhance the bioavailability due to its low solubility [4,5].

To improve drug dissolution and bioavailability of sparingly soluble drugs, there are different chemical or formulation approaches. Among the various strategies to increase the amount of dissolved drug at the absorption site, solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drug. The SD provides a promising way to increase the solubility and dissolution rate of poorly soluble drugs. There are different methods for preparation of SDs. SD is most successful technique as it is simple, economic, and advantageous to enhance dissolution rate [6-14].

The buccal route has high acceptance due to avoidance of first pass metabolism and possibility of being accessible for controlled drug release. Buccal patches are preferred over other mucoadhesive dosage forms in terms of flexibility and patients comforts and their ability to localize the dosage form in specific regions to enhance drug bioavailability. Buccal delivery of drugs overcomes deficiencies associated with the latter mode of dosing. Problems such as high first - pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route. It is also possible to administer drugs to patients who cannot be dosed orally [15-19].

The present investigation is for improvement of the solubility and dissolution rate of CLZ by forming a SD with polyethylene glycol 6000 (PEG 6000) and development of sustained-release mucoadhesive buccal patch of it. The purpose of preparing a mucoadhesive buccal patch of CLZ is to make the drug available in a soluble form in the mouth, which would facilitate its absorption from the buccal cavity. This would help to overcome its first-pass metabolism and thereby improve bioavailability.

METHODS

Materials

CLZ was supplied as a gift sample by Twilight Litaka Pharmaceuticals Pvt. Ltd, Pune, India. Hydroxyl propyl methyl cellulose (HPMC) K4M were gifted from Colorcon Pharmaceuticals (Bangalore, India). Carbopol 974 was gifted by Oxford chemicals (Mumbai, India).

Drug characterization

Melting point and UV spectrophotometric study (Varian Carry 100, Australia) of CLZ was carried out.

Solubility

CLZ solubility studies were performed by adding excess amounts of CLZ to water and analyzed using UV spectrophotometer.

Stability in solvents

The stability of CLZ was checked by using various solvents water, phosphate buffer pH 6.8, 0.1 N HCl.

Phase solubility studies

An excess amount of CLZ was added to a conical flask containing aqueous solutions of PEG 6000 in increasing concentration (1%, 2%, 3%, 4% and 5% w/v). At equilibrium after 72 hrs, aliquots were withdrawn, analyzed by UV spectrophotometer at 280 nm.

Preparation of SD [15-19]

SD were prepared at 1:0.25, 1:0.5, 1:1, 1:1.5, 1:2, 1:3, 1:5 ratios by physical mixtures (PM) solvent evaporation (SE), co-grinding (COG), co-precipitation (COP), kneading (KN), closed melting, and spray drying method (SpD).

Characterization of SD*Percent drug content and yield study**In-vitro release study*

In vitro release studies of CLZ from SD (equivalent with 250 mg) were studied in distilled water and phosphate buffer (pH 6.8), at 37±0.5°C and 75 rpm, using USP I dissolution test apparatus (basket type) (TDT-08L Electrolab, Mumbai, India).

Fourier transform infra-red spectroscopy study (FTIR)

The scanning range used was 4000-500/cm.

Powder X-ray diffraction study (PXRD)

XRD (Philips PW 1729, Netherlands) was employed using over 2θ range of 5-50°.

Differential scanning calorimetry study (DSC)

DSC (Lab Mettler Stare SW 9.20, Switzerland) was used.

Stability study of SDs

The selected SDs were packed in amber- colored bottles, stored at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for 3 months.

Formulation of buccal patches

The formulation of buccal patch is carried out using HPMC K4M and carbopol 974. The plasticizer used was propylene glycol. The patch consists of SD (equivalent to 250 mg of CLZ). All patches were prepared by solvent casting method [17,20].

The concentration of HPMC K4M was varied from 1% to 4% and 2% to 5% for carbopol 974. The concentration of plasticizer was varied from 10% to 15% for the patch (Table 1).

Tissue preparation

The goat esophageal tissue was obtained, stored in isotonic phosphate buffer (pH 7.4) and opened longitudinally and rinsed with same. The excised mucosa was immersed in isotonic saline at 60°C for 1 minute then the epithelium was peeled away from connective tissue.

Evaluation

Randomly five patches of 10 mm size (1 × 1 cm²) were selected.

Patch thickness and mass

The thickness was determined by micrometer screw gauge and weight uniformity on an electronic balance.

Surface pH

The patches were left to swell on 2% (w/v) agar plate for 2 hrs on the surface of agar plates then pH was measured with pH paper.

Folding endurance test

This test was done by repeatedly folding the patch at the same place up to maximum 200 times or till it broke.

Swelling index

The weight and diameter of original patches were determined, placed on the surface of 2% agar gel plate. The percentage swelling (%S) was calculated using the following equation:

$$\%S = (W_t - W_0 / W_0) * 100$$

W_t is weight of the patch after time t and W₀ is the initial weight at zero time.

Vapor transmission rate test (VTR)

The glass bottle filled with 2 g anhydrous calcium chloride, an adhesive (Feviquick) spread across its rim, was used in the study. The patch was fixed over the adhesive, and the assembly was placed in a constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37±2°C. The vapor transmission rate was obtained as follow:

$$VTR = (\text{Amount of moisture transmitted}) / (\text{Area} \times \text{Time})$$

***In-vitro* mucoadhesive strength**

The strength of the bond formed between the patch and mucosa membrane excised from goat mucosa was determined using two-arm balance method. The following parameters were calculated from the bioadhesive strength:

$$\text{Force of adhesion (N)} = (\text{Bioadhesive strength (g)} \times 9.81) / 1000$$

$$\text{Bond strength (Nm}^{-2}\text{)} = \text{Force of adhesion} / \text{Disk surface area}$$

***In-vitro* residence time**

The fresh goat mucosa was fixed in the inner side of the beaker; above 2.5 cm from the bottom, with cyanoacrylate glue. One side of each patch was wetted with one drop of phosphate buffer (pH 6.8) and pasted to the goat mucosa by applying a light force with a fingertip for 30 seconds. The beaker was filled with 500 mL of isotonic phosphate buffer (pH 6.8) and was kept at 37±1°C. After 2 minutes, a 50 rpm stirring rate was applied to simulate the buccal cavity environment, and patch adhesion was monitored up to 8 hrs. The time required for the patch to detach from the mucosa was recorded as the mucoadhesion time.

Content uniformity

The buccal patch (1 × 1 cm²) was dissolved in 100 ml of phosphate buffer (pH 6.8) for 6 hrs under occasional shaking.

Table 1: Composition of CLZ mucoadhesive buccal patch

Component	Formulation batch code													
	FH1	FH2	FH3	FH4	FH5	FH6	FH7	FC1	FC2	FC3	FC4	FC5	FC6	FC7
SD equivalent to CLZ (mg)	250	250	250	250	250	250	250	250	250	250	250	250	250	250
HPMC K4M (%)	1	1.5	2	2.5	3	3.5	4	-	-	-	-	-	-	-
Carbopol 974 (%)	-	-	-	-	-	-	-	2	2.5	3	3.5	4	4.5	5
PEG (%)	10	10	10	10	10	10	10	13	13	13	13	13	13	13

HPMC: Hydroxyl propyl methyl cellulose, CLZ: Chlorzoxazone, PEG: Propylene glycol, SD: Solid dispersions

In-vitro release study

The release study was done in the Keshery-Chien diffusion cell using phosphate buffer (pH 6.8). For optimized batches, egg membrane and goat mucosa were used.

Stability study of buccal patches

The selected patches were packed in aluminum then in amber-colored bottles, stored at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for 3 months.

RESULTS AND DISCUSSION**Drug characterization**

Melting point of CLZ was found in the range of 191°C-192°C.

The maximum absorbance of CLZ found at 280 nm.

Solubility

Solubility of CLZ in water was found to be 25.58 µg/ml.

Stability in solvents

CLZ was stable in solvents water, phosphate buffer pH 6.8, 0.1 N HCl.

Infra-red spectroscopy

The FTIR spectra analysis of CLZ showed, the characteristic peaks for specific structural groups were observed at wave numbers 3587.98, 3221.36, 3066.96, 2901.12, 1765.57, 1623.81, 1582.71, 1356.98, 850.02, 766.25 cm⁻¹ confirming the purity of drug as per established standards.

Phase solubility study

This study show A₁ type curve, the slope was 0.03672, stability constant (K_s) was 105.30, value of R² was 0.9987, Gibb's free energy of transfer (ΔG_{tr}^o) was -17.65 joules/mol. The negative sign of Gibb's free energy of transfer indicates the spontaneous nature of CLZ solubilization.

The results of saturation solubility study indicated that maximum increase in solubility in ratio 1:1. The KN method showed maximum saturation solubility.

Percent practical yield and drug content

The practical yield was in the range of 93.54±2.36% to 98.73±1.34% and drug content ranged between 89.97±3.01% and 98.27±1.58.

In-vitro release study

The *in-vitro* release of SDs showed a significant increase in drug release, in comparison with pure crystalline CLZ in both dissolution medium (Fig. 1). The order of dissolution enhancement by SD is KN > COG > PM > SpD > SE > COP > CM (Table 2).

FTIR

The IR spectra of SD showed characteristic peaks of CLZ are at the same wave number. Indicating no interactions of CLZ with PEG 6000.

PXRD

The lack of the numerous distinctive peaks of CLZ in XRD pattern of SDs PM, KN and COG demonstrated that a high concentration of CLZ was dissolved in carrier matrix in an amorphous state (Fig. 2).

DSC

In DSC curve of CLZ and PEG 6000 (Fig. 3) sharp endothermic peaks were observed at 191.16°C and 62.7°C. DSC curve of SDs PM, KN, COG (Fig. 3) showed position of the endothermic peak is shifted at 58°C and intensity of peak is reduced. It might be due to the amorphous form of CLZ in SD or dissolution of crystalline CLZ into the molten carrier.

Stability study of SD

These studies conclude that there was no degradation.

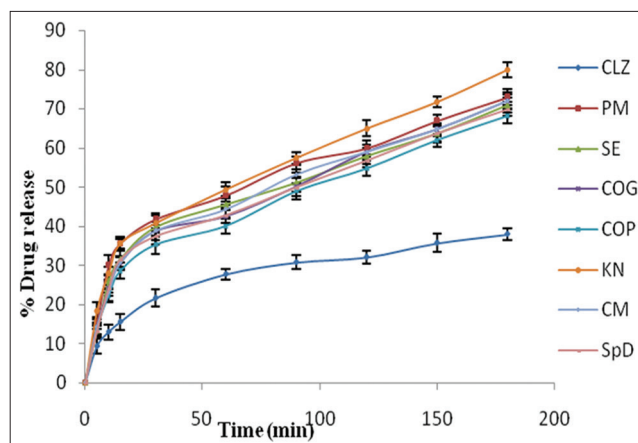


Fig. 1: Release profile of all solid dispersions in distilled water

Table 2: Physicochemical, mucoadhesive and *in-vitro* release study of buccal patches

Formulation code	Drug content±SD* (%)	<i>In vitro</i> residence time±SD* (hr)	Drug release after 8 hrs on cellophane±SD* (%)
Placebo H	-	3.64±0.49	-
FH1	98.97±0.21	3.08±0.56	78.38±1.721
FH2	97.38±0.18	3.10±0.82	75.61±2.309
FH3	98.28±0.13	2.73±0.67	76.58±2.367
FH4	99.43±0.14	3.95±0.39	87.46±2.249
FH5	101.19±0.14	3.42±0.11	76.09±2.413
FH6	97.51±0.02	3.39±0.51	73.32±2.439
FH7	95.35±0.81	2.95±0.39	70.47±1.973
Placebo C	-	3.82±0.26	-
FC1	96.13±0.33	3.67±0.37	75.69±1.998
FC2	99.92±0.26	3.17±0.28	82.52±1.888
FC3	98.68±0.62	2.25±0.21	78.8±2.568
FC4	99.34±0.15	3.63±0.33	85.96±2.316
FC5	98.90±1.11	2.92±0.69	75.03±2.209
FC6	100.38±0.41	2.86±0.66	72.31±2.369
FC7	99.65±0.20	3.34±0.15	70.53±2.508

*Average of three determinations, ±SD: Standard deviation. n=3

Buccal patch

The concentration of HPMC K4M and carbopol 974 were finalized as 2.5% and 3.5% respectively, as it showed good results. The concentration of plasticizer was 10% and 13% for the patch of HPMC K4M and carbopol 974, respectively.

SD prepared by KN method showed maximum release profile, so, it was selected for patch formulation.

The surface pH for all patches was within the desirable 6-7 units which are near to neutral pH and hence no mucosal irritation would be expected.

The folding endurance recorded for all patches were more than 200. The swelling index after 5 hrs was in the range of 34.96±2.81 to 64.49±6.57. The higher swelling index would result in excessively increased surface area which could result in unmanageable faster release of the drug and also may cause patient discomfort due to occupying of larger space in the oral cavity and chances of dislodgement.

In vapor transmission, the formulation batches FH1, FH4, FH7, FC1, FC5, FC7 were indicate less vapor transmission as compared to other batches on day 7. The highest vapor permeation $1.64 \times 10^{-3} \pm 0.15 \times 10^{-3} \text{ g cm}^{-2} \text{ hr}^{-1}$ was found with batch FH6 on day seven. While less permeation $0.65 \times 10^{-3} \pm 0.26 \times 10^{-3} \text{ g cm}^{-2} \text{ hr}^{-1}$ was found on day seven with patch FH7.

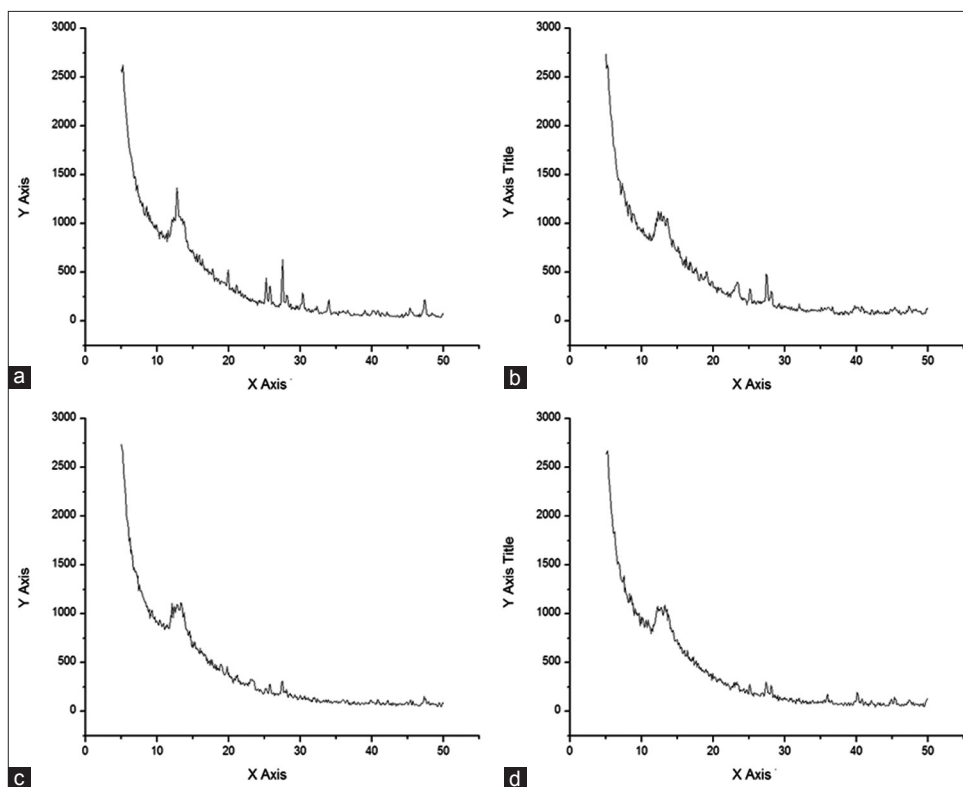


Fig. 2: Powder X-ray diffraction pattern of: (a) Chlorzoxazone, (b) physical mixtures, (c) kneading and (d) co-grinding

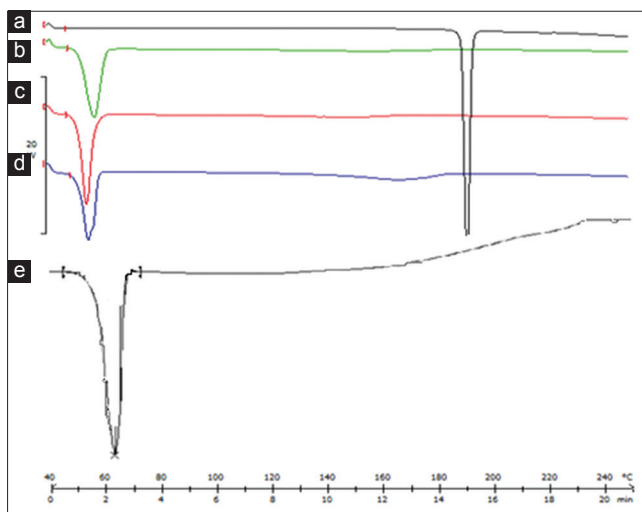


Fig. 3: DSC curves of: (a) Chlorzoxazone, (b) physical mixtures, (c) co-grinding, (d) kneading and (e) polyethylene glycol 6000

The *in vitro* residence time was found in the range of 2.73 ± 0.67 to 3.95 ± 0.39 hrs. FH6 it was found to be maximum.

The drug content in the patches was found in the range of 95.35 ± 0.81 and $101.19 \pm 0.14\%$. The optimized batches FH4 and FC4 showed 87.46% and 85.96% CLZ release, respectively from cellophane membrane. From egg membrane, 83.84% and 82.16% and from goat mucosa, 81.95% and 79.97% CLZ released, respectively for FH4 and FC4. All the release profile follows Peppas model. The release profile of CLZ from patches was shown in Figs. 4 and 5.

Bioadhesive strength of the batch FH4 and FC4 was found to be 11.32 ± 2.0 g and 9.58 ± 2.0 g. The force of adhesion was 0.0942 N, 0.0645 N and bond strength 546.74 Nm^{-2} , 463.27 Nm^{-2} , respectively for FH4 and FC4 batches.

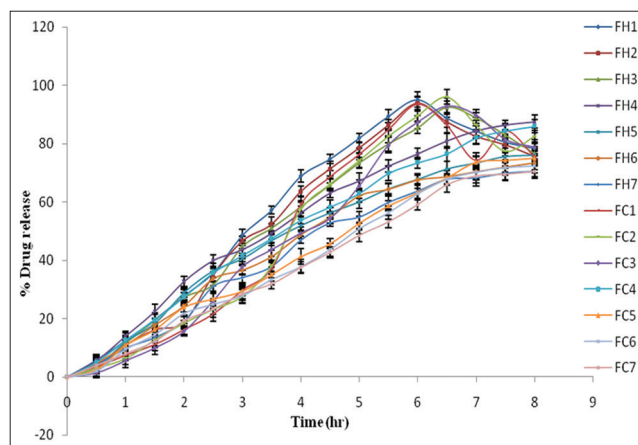


Fig. 4: Release profile of chlorzoxazone from buccal patches on cellophane membrane

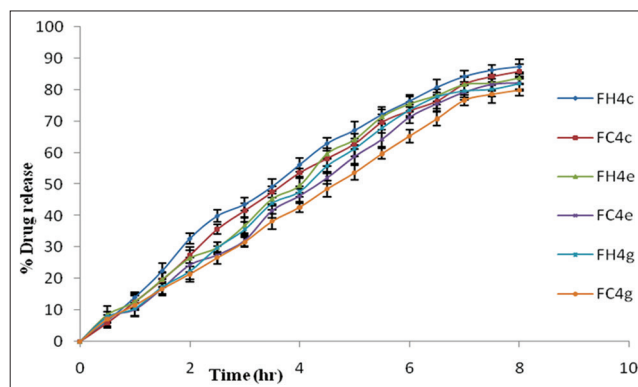


Fig. 5: Release profile of chlorzoxazone from optimized batches of buccal patch on cellophane, egg membrane and on goat mucosal membrane

The IR spectra of the patch showed the same absorption bands as the SD, illustrating on interaction.

Stability study of buccal patch

No significant changes were observed in drug content; IR data indicated no interactions of CLZ with the excipients.

CONCLUSION

CLZ is centrally acting skeletal muscle relaxant, insoluble in water. SD with carrier PEG 6000 was prepared to enhance the dissolution rate. Phase-solubility studies indicate significantly increase in solubility. The SDs were prepared by different methods and characterized. These techniques revealed distinct loss of drug crystallinity in the formulation accounting for enhancement in dissolution rate [20]. The SD methods showing best *in vitro* drug release profile were selected in the further development of mucoadhesive buccal patches. A buccal patch has been developed using two mucoadhesive polymers, i.e., HPMC K4M and carbopol 974. The patches were evaluated for the physicochemical, mechanical and drug release characteristics. The optimized patches showed good mechanical and physicochemical properties to withstand the environment of oral cavity. The *in-vitro* permeation study showed that patches could deliver drug to the oral mucosa for a period of 8 hrs [21]. The results indicate that suitable bioadhesive buccal patches with good permeability could be prepared. The batches FH4 and FC4 showed 81.95% and 79.97% permeated through goat mucosa membrane in 8 hrs. The physicochemical interactions were investigated by FTIR, showed no any evidence of interactions and were present in an unchanged state. The stability study for SD and buccal patch carried out revealed that were stable for a period of 3-month.

REFERENCES

- Dressman JB, Vertzoni M, Goumas K, Reppas C. Estimating drug solubility in the gastrointestinal tract. *Adv Drug Deliv Rev* 2007;59(7):591-602.
- Löbner R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. *Eur J Pharm Biopharm* 2000;50(1):3-12.
- Zakeri-Milani P, Barzegar-Jalali M, Azimi M, Valizadeh H. Biopharmaceutical classification of drugs using intrinsic dissolution rate (IDR) and rat intestinal permeability. *Eur J Pharm Biopharm* 2009;73(1):102-6.
- Guneri T, Taneri F, Ertan G. Studies on sustained release matrix systems of chlorzoxazone. *Acta Pharm Turcica* 2005;47:39-51.
- Reddy P. Simultaneous estimation of nimesulide and chlorzoxazone in pharmaceutical formulations by a RP-HPLC method. *Int J ChemTech Res* 2009;1(2):283-5.
- Fawaz F, Bonini F, Guyot M, Bildet J, Maury M, Laguency AM. Bioavailability of norfloxacin from PEG 6000 solid dispersion and cyclodextrin inclusion complexes in rabbits. *Int J Pharm* 1996;132:271-5.
- Van den Mooter G, Augustijns P, Bleton N, Kinget R. Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. *Int J Pharm* 1998;164:67-80.
- Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm* 2000;50(1):47-60.
- Prajapati BG, Patel MM. Conventional and alternative pharmaceutical methods to improve oral bioavailability of lipophilic drugs. *Asian J Pharm* 2007;1(1):1-8.
- Rao M, Mandag Y, Thanki K, Bhise S. Dissolution improvement of simvastatin by surface solid dispersion technology. *Dissolution Technol* 2010;27:37-4.
- Breitenbach J, Schrof W, Neumann J. Confocal Raman-spectroscopy: Analytical approach to solid dispersions and mapping of drugs. *Pharm Res* 1999;16(7):1109-13.
- Amrutkar PP, Patil SB, Tadarwal AN, Wagh MA, Kothawade PD, Surawase RK. Design and evaluation of taste masked chewable dispersible tablet of lamotrigine by melt granulation. *Int J Drug Deliv* 2010;2:183-91.
- Shimpi S, Chauhan B, Mahadik KR, Paradkar A. Preparation and evaluation of diltiazem hydrochloride-Gelucire 43/01 floating granules prepared by melt granulation. *AAPS PharmSciTech* 2004;5(3):e43.
- Patil S, Kuchekar B, Chabukswar A, Jagdale S. Formulation and evaluation of extended-release solid dispersion of metformin hydrochloride. *J Young Pharm* 2010;2(2):121-9.
- Patel VM, Prajapati BG, Patel MM. Effect of hydrophilic polymers on buccoadhesive Eudragit patches of propranolol hydrochloride using factorial design. *AAPS PharmSciTech* 2007;8(2):Article 45.
- Wong CF, Yuen KH, Peh KK. Formulation and evaluation of controlled release Eudragit buccal patches. *Int J Pharm* 1999;178(1):11-22.
- Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive buccal patches of miconazole nitrate: *In vitro/in vivo* performance and effect of ageing. *Int J Pharm* 2003;264(1-2):1-14.
- Peh KK, Wong CF. Polymeric films as vehicle for buccal delivery: Swelling, mechanical, and bioadhesive properties. *J Pharm Pharm Sci* 1999;2(2):53-61.
- Junginger HE, Hoogstraate JA, Verhoef JC. Recent advances in buccal drug delivery and absorption – *In vitro* and *in vivo* studies. *J Control Release* 1999;62(1-2):149-59.
- Jagdale SC, Hable AA, Kuchekar BS, Chabukswar AR. Improvement of dissolution rate of chlorzoxazone by solid dispersion technique and development of buccal patch. *J Appl Solut Chem Model* 2013;2(2):145-57.
- Jagdale SC, Mohanty P, Chabukswar AR, Kuchekar BS. Dissolution rate enhancement, design and development of buccal drug delivery of darifenacin hydroxypropyl β -cyclodextrin inclusion complexes. *J Pharm (Cairo)* 2013;2013:983702.