7. Summary and Conclusion

Without any hesitations, we are at a phase where we need improved formulations and treatments for combating life threatening diseases. The ongoing research against this endeavouring battle has lead to more breakthroughs in development of vital therapies but lack of efficient drug delivery systems many-a-times become a rate limiting step in efficient transfer of them in practice. Moreover, developing systems that can epitomize objectives like increasing therapeutic efficacy and enhancing patient compliance would be of prodigious concern in improving therapeutic treatment.

The present research was envisaged for developing PR formulations for time-controlled therapeutics such as early morning chronological attacks of RA, BA, VA etc. A numerous chronological conditions show early morning disturbances and every single pathological condition is being treated by different drugs. Hence, there is a wide range of drugs which need to be fabricated in the form of PR formulations. Undoubtedly, various researchers have developed the PR formulations with different compositions employing different model drugs. However, alteration of a drug candidate in an already developed formulation many-a-times alters the formulation attributes which may not always be within the desired specification limits due to the change in drug properties. In practical terms, it is often observed that separate drugs require separate development/optimization; entailing extra time and resources which would have been saved if it were a platform technology. Hence, it was thought of interest to develop a single PR platform technology which can accommodate diverse kind of drug molecules and still exhibit same lag time/release profile. Quality by Design (QbD) is one of the approaches to obtain the robust quality product which was explored here for the development of robust platform formulation. To exclusively check robustness of the platform formulation, total six drugs, i.e. PRS (RA and BA), MPR (BA), DIL (RA), DIL (VA), NIF (VA) and LOR (RA), were selected based on their wide physicochemical properties and mentioned indications. Since time to achieve peak effect for all selected candidates is about 1-3 h, the lag time was targeted between 4-6 h so that night time administration of the PR formulation will release the drug only after midnight to exhibit peak effect early in the morning. The most common and most acceptable type of dosage form i.e. solid oral tablet formulation was opted to achieve the stated target. Particularly, the research was undertaken for compression coating and

pan coating technology owing to their wide popularity, applicability and ease of scalability.

Firstly, the development was started with compression coating technology considering its advantages like solvent-less and continuous processing which is beneficial in terms of formulation stability and production viability. Here, PRS was selected as a model drug and the development was commenced by employing comprehensive QbD approach. First of all, the QTPP elements were established – the key element was 4-6 h of lag time followed by burst release profile i.e. >85% within 30 min. The QTPP elements formed the basis for identification of CQAs followed by risk assessment of critical formulation and process parameters. The impacts of critical formulation/process parameters having high risk of failure on drug product attributes were investigated thoroughly in order to mitigate the future risk. Basically, the formulation comprised of two portions viz. an IR core tablet which was surrounded by a rigid outer coat. The core tablets were prepared using classical swelling excipients chosen scrupulously. The core tablets, when characterized for *in vitro* release testing, exhibited >85% drug release within 15 min and therefore construed as fast dissolving IR tablets. Subsequently, the fabrication of outer coat was initiated in order to obtain the desired lag time followed by burst release profile. Since the main target of final formulation was to obtain the time-controlled lag time, it was foremost decided to fabricate the outer coat with pH-independent excipients only. Apparently, the lag time of a PR formulation can be contrived by varying the outer coat composition by altering the mixture of water soluble and water insoluble fractions. Typically, EC N10 was predominantly selected as pH-independent water insoluble material to fabricate the rupturable outer coat.

Subsequently, the preliminary studies were carried out for the selection of optimal lubricant, glidant and hydrophilic additive. Initially variegated lubricants and glidants such as MgSt, SSF, talc, colloidal SiO_2, glyceryl behenate, PEG 6000 and stearic acid, were investigated to understand their effects on lag time by changing their concentrations in outer coat. The study revealed that each selected lubricant/glidant, if present even at concentration as low as 0.25% w/w, significantly reduced the lag time of compression coated EC tablets. Amongst selected glidants and lubricants, the most detrimental effects were observed with the most popular glidant i.e. colloidal SiO_2 and the most lubricant i.e. MgSt. The combined effect of colloidal SiO_2 and MgSt just

converted the PR formulation into an IR formulation with almost complete removal of lag time, and thus the most popular glidant-lubricant combination was found utterly inappropriate for further development. On the other hand, relatively less popular lubricants and glidants (i.e. talc, SSF, stearic acid, PEG 6000 and glyceryl behenate) were found to be less injurious on lag time. Specifically, talc-SSF combination, which exhibited rather less impact on lag time amongst all, was chosen for further development of PR CCTs.

Further, the effects of several hydrophilic additives (viz. HPMC E5, HPC EF, HPC SSL, povidone K30, COP, PEG 4000, lactose and mannitol) on the lag time of compression-coated EC tablets were investigated by changing their concentrations in the outer coat. Amongst the selected hydrophilic additives, freely water soluble hydrophilic fillers (i.e. lactose and mannitol) depicted intense effect on lag time and therefore simple EC-water soluble filler combinations were ruled out for further development. On the contrary, polymeric binders (HPMC E5, HPC EF, HPC SSL, povidone K30, COP and PEG 4000) were found to be rather suitable for modulating the lag time of compression-coated EC tablets, amongst which HPMC E5 exhibited the most promising results in terms of obtaining desired lag time with less variability; and hence opted for further development.

Next, several HPMC MW grades (i.e. E5, E15, E50, K100LV and K4M) were also examined to understand their effects on lag time and drug release. The CCTs of higher MW HPMCs (K100LV and K4M) demonstrated comparatively higher variability in lag time than that of low MW grades (E5, E15 and E50). With K4M CCTs, the variability in lag time significantly increased with increase in its concentration in the outer coat and at 30% w/w level slight premature release was observed before the rupture of outer coat. Thus, higher concentration of HPMC K4M in the outer coat was found inappropriate with regards to stated drawbacks. Overall, low MW HPMC (i.e. E5), which exhibited low variability in lag time (<10 %RSD viz. within USP limits) and no premature release, was found to be more efficient and therefore selected for further development.

Once all key ingredients of the formulation have been selected, further development and optimization was carried out using risk assessment by FMEA approach. Using this technique, each critical parameter was ranked for three failure

modes, i.e. seriousness of failure, how frequently they occur and how easily they can be detected, and subsequently RPN was calculated. The factors with RPN $\geq$ 40 were considered at high risk, RPN $\geq$ 20 but < 40 were considered at medium risk, and RPN < 20 were considered at low risk. The factors with medium risk category were evaluated using OFAT approach whereas those with high risk category were optimized using cCCD. Particularly, core tablet super-disintegrant amount, core tablet hardness and CCT hardness were investigated using OFAT approach whereas amount of HPMC in outer coat and coating weight were subjected to statistical optimization using CCD. The CCD model generated the design space using which an optimized HPMC concentration along with 5% weight variation limits was obtained. Finally, the updated risks of all critical formulation and process parameters were re-evaluated which were found under low risk category after optimization/implementation of control strategy.

The optimized PRS CCTs were characterized for variegated *in vitro* drug release testing such as multi-media, change in apparatus, change in agitation intensity, biorelevant dissolution testing and alcohol-induced dose dumping study. The studies revealed that except hydro-alcoholic media, all tested dissolution conditions (i.e. multi-media, change in apparatus, change in agitation intensity and biorelevant media) exhibited the 4-6 h lag time (with no significant difference) followed by burst release profile (>85% within 15 min). Similar release profile with multi-media dissolution manifested the developed CCT as pH-independent in nature; akin release behaviour with different apparatus as well as with different agitation deduced that the lag time was robust enough and not influenced by change in hydrodynamics; and analogous results of biorelevant media (FaSSGF, FaSSIF, and FeSSIF) strongly anticipate promising *in vivo* performance. Conversely, alcohol-induced dose dumping study revealed that up to 10% v/v alcohol concentration, the lag time was found within desired 4-6 h of specification limits, but with further increase in alcohol concentration, i.e. $\geq$20% v/v, the formulation failed to demonstrate desired lag time. Typically, the lag time was progressively decreased with increase in alcohol concentration. Overall, the developed CCT was found to be sensitive to hydro-alcoholic media and hence associated risk has to be appropriately mentioned on the label as 'not to be co-administered along with alcohol'. Further, the developed CCTs were also subjected to curing study by exposing them at 60°C for 24 h and subsequently analyzed for hardness, assay and drug release. All results were found within their respective

specification limits with no distinguishable difference before and after curing. Thus, no effect of curing was observed and it can be said that the outer coat polymers did not undergo internal cross-linking upon storage. The optimized PRS CCTs were finally exposed to accelerated (40±2°C/75±5% RH) and long term (25±2°C/60±5% RH) stability testing for three months and characterized for hardness, assay and drug release. Since all results were found within their respective specification limits, the CCTs were found to be stable under the selected packaging material and stated storage conditions.

After ensuring desired results with developed PRS CCTs, other selected candidates, i.e. MPR, DIC, DIL, NIF and LOR, were one-by-one incorporated into the optimized formula with the replacement of PRS. Here, DIC and DIL exhibited poor flow with final compression blends. Hence, both APIs were first converted into the granular form using water as a granulating agent and subsequently used to prepare compression blends. Such granular compression blends were thereafter employed for preparation of core tablets. On the other hand, NIF and LOR are the poorly soluble compounds which were deliberately chosen for thorough assessment of robustness of PR formulation and to render it as a platform technology in real sense. The enhancement of solubility/dissolution rate of both of these APIs was carried out using solid dispersion approach. Several hydrophilic polymers, such as povidone K30, COP, HPMC, PEG 6000, etc., were investigated for preparation of NIF solid dispersion. Out of them, NIF-COP binary system prepared using solvent evaporation technique was found to be an ASD which was found optimal for preparation of NIF core tablets. Similarly, LOR ASD was also prepared using solvent evaporation technique by employing MEG as pH-modifier and HPMC E5 as hydrophilic carrier. Both ASDs were further employed for preparation of respective core tablets. All core tablets were prepared by keeping the formulation and process parameters as similar as possible to the PRS core tablets. Here, the quantity of lactose was adjusted according to individual drug requirements in order to maintain constant tablet weight. In case of LOR, lactose was replaced with mannitol for preparation of core tablets since it was reviewed that there is a possibility of interaction between lactose and MEG which was employed for formulation of LOR ASD. All core tablets were further subjected to *in vitro* drug release testing which demonstrated >85% drug release within 15 min for each of MPR, DIC, DIL and LOR tablets and >85% drug release within 30 min for NIF tablets. Thus, all core tablets were found to be fast dissolving IR tablets. Consequently, all five core

tablets were processed for compression coating using developed PRS formula and subjected to variegated *in vitro* characterizations as performed for PRS CCTs. Same as PRS CCTs, all other CCTs also exhibited precise lag time followed by burst release pattern. After completion of lag time, >85% drug release was observed within 15 min for each of MPR, DIC, DIL, and LOR CCTs; whereas CCTs of NIF depicted >85% drug release within 30 min. The lag time of all drug CCTs were found to be within 4-6 h with all tested dissolution conditions (i.e. multi-media, change in apparatus, change in agitation intensity and biorelevant media) except hydro-alcoholic media. The analogous results of all three biorelevant media once again anticipate promising *in vivo* performance for all drug CCTs. The results of hydro-alcoholic media were also in-line with those of PRS CCTs, entailing pertinent instructions to be mentioned on the label. Convincingly, all drug CCTs exhibited no effect of curing as well as found stable (no change in appearance, hardness, assay, or drug release) under the selected packaging material and stated storage conditions.

Succinctly, the developed CCT formulation exhibited robust 4-6 h of lag time followed by burst release profile with diverse kind of drug molecules and varying dissolution conditions. The release profile remained robust enough even after employing different formulation approaches in fabrication of varied core tablets on account of diverse drug properties. The lag time was found to be explicitly pH-independent as well as unaffected by change in hydrodynamics. The analogous results of biorelevant dissolutions prudently anticipate promising *in vivo* performance. All of these feats would not be possible without implementation of the QbD tools amalgamated with risk management approaches which have inclined to divulge the degree of improvement for building quality traits inside the product. In nutshell, the developed CCT can be qualified as time controlled PR platform formulation since all the drugs taken here have prudently sufficed the purpose by achieving desired lag time/release profile. It is strongly expected that the developed CCT can also extend its arms to several other APIs such as salbutamol (BA), terbutaline (BA), glucocorticoids (BA/RA) etc. and thereby benefit patients with rather rationalised chronodelivery systems; however human clinical trials are obligatory to prove the clinical usability of the developed formulations.

After developing time-controlled PR platform formulation using compression coating technology, pan coating technology was also explored to develop PR

formulations. Our prime purpose was to compare the process capability between compression coating and pan coating technology. Therefore, the development of PR PCT was carried out by keeping the formulation ingredients as similar as possible to the developed CCT formulation without any change in core tablet composition. Thus, previously formulated core tablets were subjected to pan coating using EC N10 and HPMC E5 as functional polymers in a ratio similar to optimized CCT formulation with DBS as a plasticizer. Initial optimization was carried out using PRS tablets where different coating weights were applied in order to obtain 4-6 h of lag time and subsequently other core tablets were also one-by-one coated using same optimized formulation and process parameters. Here, lag time of PRS, MPR, DIC and LOR PCTs were found to be within 4-6 h whereas those of DIL and NIF PCTs were not confined to desired specification range. Hence, unlike CCT formulation, PCT formulation was not found to be a platform technology. The comparative summary of lag times obtained with CCT formulation and PCT formulations are depicted in Figure 7.1.

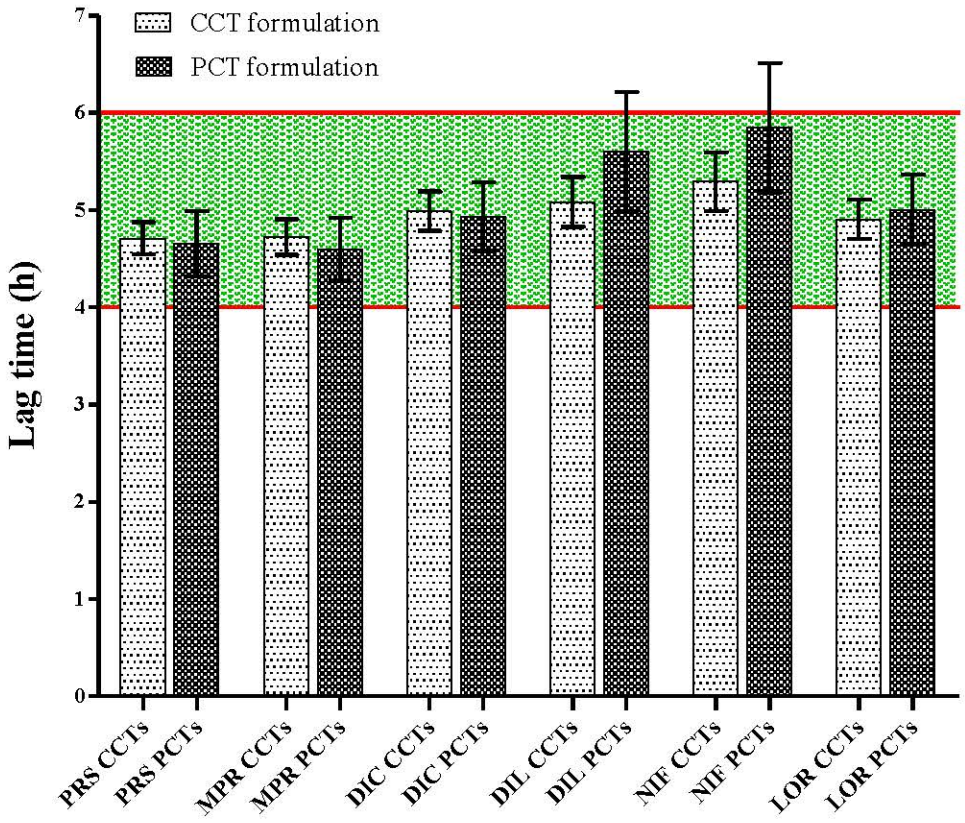

Fig. 7.1 Comparative summary of lag times obtained with CCT formulations and PCT formulations [basket apparatus; 100 rpm; 0.1 N HCl for first 2 h followed by pH 6.8 buffer; 500 mL for PRS, MPR, DIC and DIL; 900 mL for NIF and LOR; 37.0±0.5°C] (mean±95% CI; n=6).

The Figure shows that the variability in lag time of all PCT formulations was relatively higher than that of the CCT formulations; which is also another downside of PCT formulation. However, after completion of lag time, the burst release profile of each individual PCT was found to be similar to respective CCTs i.e. >85% within 15 min for PRS, MPR, DIC, DIL and LOR PCTs and >85% within 30 min for NIF PCTs. Notably, the PCT formulations were found to be more sensitive to hydro-alcoholic medium in comparison to CCT formulations viz. a mere 5% v/v concentration of alcohol shortened the lag time of all PCTs below the lower specification limit (i.e. 4 h); whereas CCT formulations withstood up to 10% v/v alcohol concentration to deliver the lag time within specification limits. Nevertheless, both, PCT as well as CCT formulations were found to be sensitive to the hydro-alcoholic medium in a greater or lesser extent and so associated risk has to be appropriately mentioned on the label. Further, all PCTs were evaluated for curing study and short term stability testing according to ICH guidelines which exhibited negligible change in either of appearance, hardness, assay or drug release. Thus, no effect of curing was observed and the formulations were found stable under the selected packaging material and stated storage conditions.

After having desired results with *in vitro*, DIC PCT was selected as a model formulation and evaluated for *in vivo* pharmacokinetic study using NZW rabbits in order to compare the pharmacokinetics of developed PCT formulation (test) with that of the conventional IR formulation i.e. uncoated DIC core tablet (reference). After oral administration, the blood samples were withdrawn at suitable time intervals from marginal ear vein into heparinized collection tubes which were immediately centrifuged to extract out the plasma. The plasma samples were subjected to protein precipitation and finally analyzed for drug content using previously developed bio-analytical LC-MS method in order to determine various pharmacokinetic parameters viz. C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $T_{1/2}$, Ka, Kel etc. The results revealed that the developed PCT exhibited about 4-5 h of *in vivo* lag time which thereby delayed its T_{max} accordingly. Apart from that, all other pharmacokinetic parameters (viz. C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, Ka and Kel) of developed PCT formulation were found to be in accordance with those of the conventional IR formulation; which means that the developed PCT just restricted the drug release for predetermined time and subsequently provided burst drug release similar to the IR formulation. Moreover, the geometric mean ratios of C_{max}, AUC_{0-t} and

$AUC_{0-\infty}$ at 90% CI for test (PCT formulation) to reference (IR formulation) were found to be within 0.80-1.25 limits; and thus the developed PCT formulation was found to be bioequivalent to the conventional IR formulation with only difference of lag time and thereby T_{max}. Furthermore, close proximity of Ka as well as Kel between PCT formulation and IR formulation also ruled out the possibility of differential absorption phenomenon that might have occurred due to the change in absorption sites. Overall, the developed PCT was found to be a PR formulation which exhibited 4-6 h of lag time, and subsequently provided burst drug release similar to IR formulation. Thus, developed DIC PCTs exhibited close resemblance between *in vitro* release profile and *in vivo* pharmacokinetic behaviour in NZW rabbits.

Concisely, like CCT formulation, the developed PCT formulation also exhibited distinct lag time followed by burst release profile, however, the lag times of two (i.e. DIL and NIF PCTs) out of six PCTs were not strictly confined to 4-6 h of desired specification range. Hence, unlike CCT formulation, PCT formulation was not emerged as a platform technology; which means that development of PR formulation using pan coating technology may demand separate optimization of formulation/process parameters which may vary on case by case basis. Besides, relatively higher variability in lag time of developed PCT formulations also makes it inferior in comparison to the CCT formulations. Nevertheless, large scale manufacturing of compression-coated formulations necessitates a specially designed tablet compression machine whereas that of pan-coated formulations can be easily accomplished using rather simple, more common and cost-effective pan coaters; which remains the strong points to opt for the same.

In nutshell, the developed formulations have shown PR profile with different type of drugs and therefore can be potentially helpful in the management of various chronological outbreaks. It is strongly anticipated that the developed formulations can indeed improve therapeutic efficacy of existing drug molecules and thus will become better substitutes for conventional available formulations which will ultimately benefit patients and health care system.